Importance of Nutrition

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Efficacy of Bresol Syrup in Pediatric Allergic Rhinitis
Introducing...

HiOwna-Jr.

Balanced nutritional supplement to improve physical, mental, and immune development in children

First time in India
Easy to mix nutritional supplement containing Pea protein + Colostrum + Herbal actives which offer superior nutritive benefits

Flavor
Chocolate
Strawberry

The Himalaya Drug Company
Makali, Bangalore 562 123, India
www.himalayahealthcare.com
E-mail: write.to.us@himalayahealthcare.com
Balanced nutrition is essential for maintaining good health, reducing risk of developing diseases, and healthy aging. According to recent statistics, in India alone, subclinical micronutrient deficiency has been persistent in about one-third of the 2 billion people with micronutrient deficiency. About 40% of the world’s severely malnourished children under 5 years of age are in India.

HiOwna and HiOwna-Jr., multi-ingredient nutritional health supplements of The Himalaya Drug Company, are formulated to provide overall nutritional benefits to young and elderly adults and children. HiOwna is also indicated in postoperative convalescence, prolonged illness, and stress of varied etiology. HiOwna-Jr. plays an important role in improving overall physical, mental, and immune development in children.

The role of HiOwna and HiOwna-Jr. in the management of postoperative convalescence and in maintaining health and cognition in children, respectively, are discussed in the “Clinical Insight” section of this issue. This section also features clinical reports evaluating the safety and efficacy of Bresol (tablet, syrup) in the treatment of respiratory tract infections.

Medicinal properties of herbs such as Cissus quadrangularis, Emblica officinalis, Terminalia bellirica, and Eleusine coracana are discussed in the “Herbal Notes” section. The “Patient Education” section provides information on etiology and management of tooth sensitivity. Please use the patient information leaflet order form, enclosed in the issue, to avail reprints of this information.

For any suggestions/feedback/queries, write to us at publications@himalayahealthcare.com.

Happy reading!
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For subscription requests and other communications:

The Managing Editor—Probe
Scientific Publications Division
The Himalaya Drug Company
Makali, Bangalore 562123

Email: publications@himalayahealthcare.com
Role of HiOwna, a Polyherbal Health Drink in Postoperative Convalescence: A Comparative Clinical Study to Evaluate Safety and Efficacy

Roy D, Rugvedi P


ABSTRACT

The aim of this study was to evaluate the clinical efficacy and safety of HiOwna, a polyherbal health drink in postoperative convalescence. A comparative clinical trial was conducted in 45 postoperative cases during their convalescence period. An ethics committee approval was obtained before initiation of the study. Individuals who fulfilled the selection criteria and signed informed consent forms were recruited for the study. All the individuals were given HiOwna or the comparator health drink as per the randomization—4 tablespoons of health drink mixed with warm milk or warm water, twice daily for a period of 1 month. Individuals were assessed at entry, and at the end of 15 days and 30 days. At each visit the individuals were evaluated for various parameters of postoperative signs and symptoms.

Significant improvement was observed in parameters like hemoglobin, WBC count, time taken for complete recovery and weight gain in the group receiving HiOwna as compared with the group receiving comparator health drink. HiOwna also showed comparable results with respect to recovery from pain in the incision site and time taken for patient ambulation with the comparator.

HiOwna, a natural health supplement is safe and effective in reducing undesirable sequelae of surgical injury with accelerated recovery and reduction in postoperative morbidity and overall costs.

Key Words

HiOwna, postoperative convalescence, postoperative morbidity

Introduction

From a metabolic and nutritional point of view, the key aspects of perioperative care include integration of nutrition into the overall management of the patient, metabolic control, reduction of factors which exacerbate stress-related catabolism or impair gastrointestinal function and early mobilization.¹

Major operations are commonly followed by fatigue and convalescence. The pathogenesis of early postoperative fatigue can include sleep disturbances induced by cytokines and opioids in the early period, while late fatigue persisting for up to several weeks can lead to loss of muscle tissue and function, deconditioning of cardiovascular response to exercise.² The changes in organ function are thought to be mediated by trauma-induced endocrine metabolic changes and activation of several biological cascade systems (cytokines, complement, arachidonic acid metabolites, nitric oxide, free oxygen radicals, etc).²

Therapeutic interventions to reduce catabolism, loss of muscle tissue and function may include stress reduction,
enforced early mobilization, electrical muscle stimulation, and early oral nutrition supported by pain relieving techniques to accelerate restoration of gastrointestinal motility. Furthermore, a variety of nutritional substrates, growth hormones or other growth factors may reduce catabolism and maintain muscle mass.\(^2\)

Postoperative recovery is dependent on pain, fatigue, and traditional recommendations of a long convalescence period. Reduction of the convalescence period is also highly dependent on advice from surgeons and general practitioners, but in the past such information has mostly been restrictive and based on traditions.\(^3\)

During and after surgical injury, the body undergoes profound changes in neural, endocrine, and metabolic systems in addition to alterations in organ functions,\(^4\) which may implicate in the development of postoperative complications. All surgical procedures are followed by pain, which may amplify endocrine metabolic responses, autonomic reflexes, nausea, ileus and muscle spasm, and thereby delaying restoration of function. Optimal treatment of postoperative pain is mandatory in order to enhance recovery and reduce morbidity.

Much evidence has emerged to demonstrate pronounced trauma-induced alterations in immunological systems. Major surgery causes immunosuppression with reduced delayed hypersensitivity response to recall antigen stimulation, T-cell dependent antibody response, interleukin (IL)-2 production, and human leukocyte antigen (HLA)-DR antigen expression, Interferon (IFN)-\(\alpha\) production and T-cell blastogenesis.\(^5\) The clinical consequences of preoperative and postoperative immunological changes are increased susceptibility to infective complications.\(^6\)

Nausea, vomiting, and ileus are among the most common postoperative complaints. In addition to being unpleasant these may also be important determining factors in postoperative rehabilitation. Thus, early enteral nutrition (EN) is critical in reducing posttraumatic infective complications\(^7\) and catabolism.\(^8\)

Postoperative patients experience severely disturbed sleep patterns like decrease in total sleep time, elimination of rapid eye movement sleep, and marked reduction in slow wave sleep (SWS).\(^9\) The pathogenesis of postoperative sleep disturbances is multifactorial, and includes afferent neural stimuli (surgical stress), cytokines, pain, use of opioids, noise, and awakenings during monitoring and nursing procedures.\(^10\) Traditional perioperative care involves bed rest, although it is well known that immobilization may increase the risk of thromboembolic and pulmonary complications. Furthermore, bed rest predisposes to orthostatic intolerance and instability during standing, and to an increased loss of muscle tissue and function.\(^11\) Early ambulation may improve wound healing\(^12\) and rehabilitation in order to improve outcome and reduce costs.

It has been suggested that the routine provision of oral dietary supplements in postoperative surgical patients is of benefit in terms of morbidity and length of hospital stay.\(^13\)

Oral nutrition by means of oral nutritional supplements and if necessary tube feeding offers the possibility of increasing or ensuring nutrient intake in cases where food intake is inadequate. Trauma patients with normal nutritional status have a high risk of developing septic complications and multiple organ failure. Early EN has been claimed to reduce septic complications\(^14-16\) and has been suggested to reduce the rate of multiple organ failure when initiated within 24 hours.\(^17\)

An US national database evaluation also supported the cost-effectiveness of nutritional formulae modulating immune-function. In order to reduce resource consumption and total cost, a break even infection rate was also calculated for well nourished as well as undernourished surgical patients.\(^18\) Three randomized controlled trials showed that postoperative immune modulating formulae are effective in both undernourished and well nourished gastrointestinal cancer patients. In patients undergoing gastrectomy for gastric cancer, early EN with immune-modulating formula was associated with significantly less wound-healing problems, suture failure, and infectious as well as global complications.\(^18\)

It is also found that time for wound closure can be shortened by oral antioxidant and glutamine containing supplements in trauma patients with disorders in wound healing.\(^19\)

In addition to reducing early post-transplant infections by perioperative immunonutrition the use of such immune-modulating diets over an extended period in patients with advanced liver disease may ameliorate the malnutrition-induced immune suppression and hyper-inflammatory state characteristic of these patients\(^20\) with subsequent survival benefit. Whenever possible administration of these supplemented formulae should be started before surgery and continued postoperatively for 5 to 7 days after uncomplicated surgery.\(^18\)

An immunonutritional formula enriched with arginine, fish oil, and nucleotides has proven to be beneficial
in reducing postoperative infectious complications and length of hospital stay. Studies of patients given EN supplemented with arginine or glycine after major surgery benefited from a faster recovery of immunological parameters, fewer infectious complications and a shorter hospital stay. The elimination of ileus allows the early use of EN which is an important factor in reducing the risk of infectious complications.

Nutritional supplements with varying nutrients, flavors, and tastes are available in the market as per patient preferences to benefit postoperative nutrition to control postoperative dysfunction. So, this comparative clinical study was aimed to evaluate the clinical efficacy and safety of an oral polyherbal health drink in the clinical recovery during postoperative convalescence cases.

Exclusion criteria
- Postoperative cases advised nil per oral
- Cases with intestinal obstruction, paralytic ileus, pulmonary embolism, or any severe infection
- Postoperative cases requiring observation in ICUs
- Individuals suffering from cardiac, hepatic, renal failure, or regularly on any treatment or concurrently taking medicines for any illness, etc
- Those with a strong history of food or drug allergy
- Individuals not willing to provide informed consent or abide by the requirements of the study

Study Procedure
All the eligible cases were given a detailed description about the investigational product, nature, and duration of the study. Only those who met the study requirements, signed an informed consent form, and were willing to follow instructions given by the investigator and had an updated medical history on file with the investigator who were included in the study. The investigator retained the original copy of the signed informed consent and returned a copy of the same to the enrollees.

At each follow-up visit, the investigator recorded information about any intercurrent illness or infections and concomitant medication. Any adverse events reported or observed by patients were recorded along with information about severity, date of onset, duration, and action taken regarding the study medication. Relation of adverse events to study medication was predefined as “unrelated” (a reaction that does not follow a reasonable temporal sequence from the administration of the drug); “possible” (follows a known response pattern to the suspected drug, but could have been produced by the individual’s clinical state or other modes of therapy administered to the subject); and “probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the individual’s clinical state).

Primary and Secondary Endpoints
The predefined primary endpoint was speedy recovery in postoperative convalescence. The predefined secondary endpoints for short-term safety were assessed by incidence of adverse events, and compliance to the drug therapy.
Table 1. Demographic Data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HiOwna</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.80 ± 13.08</td>
<td>44.85 ± 13.04</td>
</tr>
<tr>
<td>Number of patients (M, F)</td>
<td>25 (18, 7)</td>
<td>20 (14, 6)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Meshplasty for hernia</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>b. Placation of the sac in chylous ascites</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>c. Saphenofemoral ligation on right foot for varicose veins</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>d. Sacroplasty for filarial scrotum</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>e. Appendicectomy</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>f. Cholecystectomy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>g. Orchidectomy</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>h. Left eversion of sac in hydrocele</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>i. Hemorrhoidectomy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>j. Excision of lipoma fibroadenoma</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>k. Others (hemisectomy, hemithyroidectomy, wound debridement, gastrectomy, sphincterectomy, etc)</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2. Hematological Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HiOwna</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g %)</td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td></td>
<td>12.80 ± 0.80</td>
<td>13.15 ± 0.65</td>
</tr>
<tr>
<td></td>
<td>12.59 ± 1.71</td>
<td>12.68 ± 1.71</td>
</tr>
<tr>
<td>WBC count (% w/mm)</td>
<td>8684 ± 1085</td>
<td>8180 ± 695.8</td>
</tr>
<tr>
<td></td>
<td>8325 ± 1910</td>
<td>7325 ± 1263</td>
</tr>
</tbody>
</table>

Statistical analysis: Paired t-test, significance as compared with respective initial values. NS: not significant.

Table 3. Effect of HiOwna and Comparator Health Drinks on Biochemical Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HiOwna</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGPT</td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td></td>
<td>32.80 ± 2.22</td>
<td>33.40 ± 2.63</td>
</tr>
<tr>
<td></td>
<td>30.95 ± 3.58</td>
<td>33.15 ± 3.25</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.67 ± 0.21</td>
<td>0.73 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>0.80 ± 0.25</td>
<td>0.83 ± 0.14</td>
</tr>
<tr>
<td>Uric acid</td>
<td>4.21 ± 0.50</td>
<td>4.44 ± 0.77</td>
</tr>
<tr>
<td></td>
<td>4.67 ± 0.81</td>
<td>4.62 ± 0.51</td>
</tr>
</tbody>
</table>

Statistical analysis: paired t-test. NS, not significant; SGPT, Serum Glutamic Pyruvate Transaminase.

Table 4. Effect of HiOwna and Comparator Health Drinks on Weight Profile

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HiOwna</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Day 15</td>
</tr>
<tr>
<td></td>
<td>55.85 ± 7.09</td>
<td>57.46 ± 7.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; .001</td>
</tr>
<tr>
<td></td>
<td>Initial</td>
<td>Day 15</td>
</tr>
<tr>
<td></td>
<td>61.0 ± 8.24</td>
<td>61.65 ± 7.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; .01</td>
</tr>
</tbody>
</table>

Statistical analysis: Repeated measures of ANOVA followed by Tukey’s multiple comparison test.

Results

The demographic details of the individuals at entry are provided in Table 1. Both the groups were comparable at entry in terms of age, sex, and type of surgery. Effect of HiOwna and comparator health drinks on parameters of hemoglobin and WBC count are shown in Table 2. In the group that received HiOwna, hemoglobin significantly increased from 12.80 ± 0.80 at entry to 13.15 ± 0.65 at the end of the study (P < 0.026). The changes in the mean hemoglobin were not significant in the comparator group with mean initial values from 12.59 ± 1.71 at entry to 12.68 ± 1.71 at the end of the study.
Clinical insight

Comparator group also, the changes after trial value of 4.44 ± 0.77. In the with initial value of 4.21 ± 0.50 and uric acid, changes were not significant

Similarly for HiOwna, it was 0.73 ±0.14 with 0.21 at entry and after administration with HiOwna, it was 0.73 ±0.14 with no significant changes. Mean creatinine value was 0.67 ±

Mean weight gain in the HiOwna group was 61.10 ± 8.24 at entry, which improved to 61.65 ± 7.93 at 15 days and at the end of 30 days showed further improvement to 62.45 ± 8.29 as compared with the initial values; had a significance of P < .01 at 30 days as compared with at entry values.

Table 6. Effect of HiOwna and Comparator Health Drinks on Pain in the Incision Site

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days of Evaluation</th>
<th>Pain</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HiOwna</td>
<td>Day 0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Day 15</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Day 30</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Comparator</td>
<td>Day 0</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Day 15</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Day 30</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>

Statistical analysis: Fisher’s exact test for within the group analysis; P values mentioned in the table are with respect to day-0 observation; no statistical significance was observed for between-the-group analysis on days 15 and 30.

Table 7. Time Taken for Ambulation and Complete Recovery

<table>
<thead>
<tr>
<th>Ambulation (days)</th>
<th>HiOwna</th>
<th>Comparator</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.83 ± 0.64</td>
<td>1.44 ± 1.09</td>
<td>NS</td>
</tr>
</tbody>
</table>

| Time taken for complete recovery (days) | 8.17 ± 3.20 | 11.40 ± 3.25 | P < .002 |

Statistical analysis: unpaired t-test for between-the-group analysis.

Results for the mean WBC count (% w.mm) in the group that received HiOwna also showed significant changes from the initial 8684 ± 1085 to 8180 ± 695.8 at the end of the study. Also in group that received comparator, WBC count (% w.mm) improved from 8325 ± 1910 to 7325 ± 1263 at the end of the study. Statistical analysis performed within the group showed that level of significance was P < .001 in the group that received HiOwna and P < .026 in the group that received comparator as compared with their respective initial values.

The effect of HiOwna on biochemical parameters of SGPT, serum creatinine, and uric acid are shown in Table 3. Mean value of SGPT in the study group at entry was 32.80 ± 2.22 and after treatment was 33.40 ± 2.63 with no significant changes. Mean creatinine value was 0.67 ± 0.21 at entry and after administration with HiOwna, it was 0.73 ±0.14 with no significant changes. Similarly for uric acid, changes were not significant with initial value of 4.21 ± 0.50 and after trial value of 4.44 ± 0.77. In the comparator group also, the changes were not significant for all the 3 variables. This establishes the safety of both the formulations.

The effect of HiOwna on weight profile is shown in Table 4. In the HiOwna group, the mean weight which was 55.85 ± 7.09 at entry improved to 57.46 ± 7.5 at 15 days and further improved to 58.15 ± 7.65 at 30 days after continued administration. The level of significance was found to be P < .001 both on day 15 and day 30 as compared with initial values.

The mean weight in the comparator group was 61.10 ± 8.24 at entry, which improved to 61.65 ± 7.93 at 15 days and at the end of 30 days showed further improvement to 62.45 ± 8.29 as compared with the initial values; had a significance of P < .01 at 30 days as compared with at entry values.

Between-the-group comparisons for weight gain are shown in Table 5. The mean weight gain in the HiOwna group on day 15 was 1.62 ±1.45, which is significant with P < .04 as compared with the comparator group, which was 0.55 ± 1.36 on day 15. On day 30 the improvements in both groups were comparable with no significant changes; mean weight gain of 2.31 ± 1.55 in study group and 1.35 ± 1.93 in comparator group, respectively. This analysis clearly establishes the beneficial effect of HiOwna over the comparator in terms of weight gain.

The effect of HiOwna and comparator on pain at the incision site is shown in Table 6. In HiOwna group, 23 out of 25 individuals had no pain on day 15, which is statistically significant with P < .0001. On day 30 all the subjects in the group were free from pain in the incision site with significance of P < .0001 compared to the initial values.

In the comparator group comprising of 20 individuals, 19 of them had no pain on day 15 and all 20 were relieved of pain by the end of day 30. Results were significant with values of P < .0001 on both the intervals compared with the initial values.

The effect of HiOwna on time taken for ambulation and complete recovery after surgery is shown in Table 7. The results were compared between the groups and were found comparable with mean values of 1.83 ± 0.64 and 1.44 ±1.09 for HiOwna and comparator, respectively, for ambulation. Time taken for complete recovery was much earlier in the HiOwna group, 8.17 ± 3.20 compared with comparator group, 11.40 ± 3.25 mean values with a significance of P < .002.

Overall results suggest that HiOwna group showed better results with respect to hemoglobin, WBC count, and time taken for complete recovery along with significant weight gain compared with the comparator health drink. HiOwna health drink has comparable results with respect to recovery from pain in the incision site and time taken for patient ambulation. Other parameters like fever, nausea, and vomiting, infection at the incision site with significance of P < .0001 compared to the initial values.
site, appetite also comparatively improved in both the groups. Overall patient compliance was good and no adverse drug reactions observed or reported with both the health drinks.

Discussion

The physiological changes after routine major surgery may persist for up to several months in patients receiving established routine care. While no single technique or drug regimen has been shown to eliminate postoperative morbidity and mortality, multimodal interventions may lead to a major reduction in the undesirable sequelae of surgical injury with improved recovery and reduction in postoperative morbidity and overall costs. Oral nutrition is the physiological route of nutrient intake, is cost effective and generally safe, and should be the preferred method of nutritional support in the presence of a functioning gastrointestinal tract. Energy and protein requirements depend on body composition, clinical status, and mobility. A coordinated multidisciplinary team approach to nutritional support can reduce the incidence of feeding complications and improve the overall quality of care.

HiOwna is a poly-ingredient formulation designed to support normal physiological functioning of the nervous and cardiovascular systems, enhance natural immunity. The principal ingredients of HiOwna health drink include herbs like *Saccharum officinarum*, *Pisum sativum*, *Phoenix dactylifera*, *Emblica officinalis*, *Piper nigrum*. Additional ingredients include skimmed milk powder (kshira), soy protein isolate, maltodextrin, cocoa powder, minerals (calcium, phosphorous, iron, magnesium, zinc, chromium, selenium, molybdenum), vitamins (A, C, D, E, K, B1, B2, B6, B12, niacin, biotin, folic acid, pantothenic acid) and nature identical flavoring substance. The pharmacological actions of the ingredients in the formulation are discussed broadly under the following headings:

Antioxidant activity

*P dactylifera* fruits are ideal high-energy foods rich in carbohydrates, including dietary fiber and minerals, such as calcium, iron, magnesium, phosphorus, potassium, and zinc. Recent studies indicate that the aqueous extracts of dates have potent antioxidant and antimitagenic activity. The antioxidant activity is attributed to the wide range of phenolic compounds in dates including p-coumaric, ferulic, and sinapic acids, flavonoids, and procyanidins. Growing evidence indicates that diets rich in fruits and vegetables afford protection against chronic diseases, such as cardiovascular disease. It follows that *P dactylifera* fruits may provide a significant source of daily dietary carbohydrates.26

Various trials conducted with *S officinarum* juice provides antioxidant activity at various levels—inhibits free radical formation by reducing iron complexes, radical scavenging at both primary and secondary stages, and in membrane protection (as assayed by lipid peroxidation).27 Multiple micronutrients such as vitamins and minerals when delivered through either supplements or fortified foods were found to have a positive effect on cognition.28

Neuroprotective activity

Oxidative stress has been implicated in cognitive impairment and may be responsible for the development of Alzheimer’s disease (AD) in elderly persons. So, antioxidants having acetylcholinesterase inhibitory properties may have beneficial effects in AD. Vitamin C, present in *E officinalis* is also a good antioxidant. The neuroprotective effect of *E officinalis* may be due to antioxidant and acetylcholinesterase-inhibitory property.29

Adaptogenic activity

Adrenal glands contain large amounts of ascorbic acid and cortisol, which are relatively decreased due to stress. Trials are supportive of fruits of *E officinalis* in having adaptogenic activity.30

Enhancement of nutrient absorption and gastroprotective activity

*P nigrum*, a rich source of piperine, has been proven to increase the secretion of bile in experimental studies.31 This suggests that *P nigrum* aids in the digestion and absorption of dietary fats. *P nigrum* was found to offer protection against the gastric damage caused by gastric irritant agents that might be related to the inhibition of gastric motor activity and the stimulation of prostaglandin synthesis.32 This is indicative of the gastroprotective activity that *P nigrum* exerts.

Dietary piperine, by favorably stimulating the digestive enzymes of pancreas, enhanced the digestive capacity and significantly reduced the gastrointestinal food transit time; enhanced the bioavailability of a number of phytochemicals by inhibitory influence on enzymatic drug biotransforming reactions in the liver. Piperine’s bioavailability enhancing property is also partly attributed to increased absorption as a result of its effect on the ultrastructure of intestinal brush border.33

*E officinalis* fruit extract contains tannins, gallic acids, alkaloids,
Clinical insight

growth and repair, improves Hb levels, Milk (skimmed) contains protein nutritionally complete foods available. be described as one of the most biotransformation of IgG to IgA. 38 by increasing the level of the well reported in improving immunity officinalis immunomodulatory potential of 39 Milk can has been proved in enhancing the Juice of S officinarum/ refined sugar has been proved in enhancing the Hb levels in the blood.39 Milk can be described as one of the most nutritionally complete foods available. Milk (skimmed) contains protein that is helpful in improving better growth and repair, improves Hb levels, improves skin-health, and provides energy.60

Pea (P sativum) is a rich source of crude protein (23%), carbohydrate (54%), and contains trigonelline. Pea has been reported to have laxative activity. Pea protein (PP) is a rich source of crude protein, crude fiber, minerals, and amino acids that include arginine, histidine, leucine, methionine. Pea protein, a rich source of highly digestible protein, has very low levels of anti-nutritional factors. This unique property of pea protein provides better nutritional benefits compared to other protein supplements.41

The ingredients of HiOwna provide balanced nutrition and help in promoting overall health by their nutritive, energy boosting, digestive, antioxidant, and immunomodulatory properties. P dactylifera is a good source of nutrients and has potent antioxidant activities. P nigrum improves digestion and enhances absorption of nutrients from the gastrointestinal tract. E officinalis has potential immunomodulatory activity and protects from repeated infections. In addition to the unique botanicals, HiOwna contains various essential macro- and micronutrients that meet the nutritional demand required at various stages of physiological requirement. Proteins, carbohydrates, and fats provide energy, promote growth and development, and regulate body functions. Vitamins and minerals have a beneficial effect in meeting the additional nutritional requirement at various stages.

Other functions

juice of S officinarum/refined sugar released the immunosuppressive effects of Cr on lymphocyte proliferation and even restored the IL-2 and IFN-α production considerably.36 An experimental study conducted on mice demonstrated that the aqueous extract of E officinalis was very effective in reducing CP-induced suppression of humoral immunity.37 All the above studies indicate the immunomodulatory potential of E officinalis fruit. Skimmed milk powder is well reported in improving immunity by increasing the level of the biotransformation of IgG to IgA.38

Immunomodulatory activity

An experimental study showed that amla (E officinalis) is effective against the cytotoxic effects of chromium-induced oxidative damage of murine macrophages and resulted in an enhanced cell survival, decreased free-radical production, and higher antioxidant levels similar to that of control cells. Further, chromium (VI) treatment resulted in decreased phagocytosis and IFN-α production, while amla inhibited chromium-induced immunosuppression and restored both phagocytosis and IFN-α production by macrophages significantly.39 These findings suggest the cytoprotective and immunomodulatory potential of E officinalis fruit.

In another in-vitro study, amla relieved the immunosuppressive effects of Cr on lymphocyte proliferation and even restored the IL-2 and IFN-α production considerably.36 An experimental study conducted on mice demonstrated that the aqueous extract of E officinalis was very effective in reducing CP-induced suppression of humoral immunity.37 All the above studies indicate the immunomodulatory potential of E officinalis fruit. Skimmed milk powder is well reported in improving immunity by increasing the level of the biotransformation of IgG to IgA.38

Conclusion

This clinical study clearly shows that HiOwna, a polyherbal health drink supplement is effective in accelerating postoperative recovery. The improvement in the postoperative parameters like hemoglobin, WBC count, time taken for complete recovery, significant weight gain were much quicker and significant in HiOwna group as compared to the comparator health drink. HiOwna health drink has comparable results with respect to recovery from pain in the incision site and time taken for patient ambulation. Other parameters like fever, nausea and vomiting, infection at the incision site, and appetite also showed comparable improvement in both the groups. Overall patient compliance was good and no adverse drug reactions was observed or reported with both the health drinks. The efficacy of HiOwna can be attributed to the synergistic actions of the potent herbs and micro- and macronutrients. The ingredients of HiOwna provides balanced nutrition and help in promoting overall health by their nutritive, energy boosting, digestive, antioxidant, and immunomodulatory properties. The immunomodulatory activity enhances body immunity as evident by absence of postoperative secondary infections and healing of the wound at the incision site. Therefore, it can be concluded that HiOwna, a natural health drink supplement is safe and effective in reducing undesirable sequelae of surgical injury with accelerated recovery and reduction in postoperative morbidity and overall costs.

References

Role of HiOwna-Jr. in General Health and Cognition of Children: A Preliminary Clinical Safety and Efficacy Study

Palani D, et al.

Abstract

The present study aimed to evaluate the clinical efficacy and safety of a polyherbal formulation (HiOwna-Jr.) on general growth, health, and cognition in children.

An open clinical trial was conducted in children after approval from the ethical committee. Fifty children (both male and female) aged between 2 and 10 years and whose parent or guardian had given the consent to participate in the clinical study were included in the trial. Subsequently, all children underwent a simple physical and systemic examination. They were advised to consume the formulation, defined by the protocol, as follows: Children in the age group of 2 to 6 years were instructed to take 12.5 g of the formulation, while those in the age group of 7 to 10 years were instructed to take 25 g of the health drink along with milk orally, twice-daily, for a period of 2 months. All enrolled children were monitored at monthly intervals for a period of 2 months for the effect of the health drink as well as for any reported or observed adverse effects. At each visit, the children were evaluated for general health and growth. In addition, cognition was evaluated in children aged between 5 and 10 years.

Height, weight, body mass index, and general health improved with the use of HiOwna-Jr. as determined by reduction of the frequency of respiratory illness and improved appetite in children aged between 2 and 10 years. Cognition parameters such as attention, memory, and concentration in children aged between 5 and 10 years also showed beneficial results. All the children preferred the formulation and completed the study. Overall compliance toward the study was good. No adverse effects were either reported or observed.

Therefore, it can be concluded that HiOwna-Jr., given in addition to regular balanced diet, helps maintain adequate natural linear growth, enhance immunity, and favorably, modify cognition in children.

Key Words
Cognition, growth, HiOwna-Jr.

Introduction

Micronutrient deficiencies compromise the health and development of many children worldwide. They can negatively affect their physical and mental developments and increase susceptibility to infections.1–3 Micronutrient interventions, such as multiple micronutrients, might benefit the health and development of children as compared to single micronutrient. Food fortification is a practical way to provide extra micronutrients to children. Recent estimates indicate that 20% of young children are underweight, 32% are stunted, and 10% are wasted, which increases the mortality and morbidity rate and also hinders them from meeting their full potential.4,5

Intercurrent illness plays a significant role when growth and weight gain are marginal in the baseline state. Specifically, intercurrent infection may lead to poor intake of food stuffs because of weariness and vomiting, or may produce a hypermetabolic state owing to fever. The immunocompromised are more prone to gastrointestinal (GI) infections, and it is important to consider...
opportunistic infections caused by Gram-negative, staphylococcal, fungal, and parasitic infestations. Patients who have disabilities may convalesce more slowly due to their hypostatic state and inability to rid themselves of respiratory secretions. Urinary tract infections (UTIs) are more common because of a neurogenic bladder associated with central nervous system (CNS) and spinal conditions, or because of congenital urologic anomalies. Other intercurrent conditions include inflammatory conditions such as collagen vascular disease, inflammatory bowel disease, and malignancy.6

Undernutrition, growth failure, overweight, micronutrient deficiencies, and osteopenia are nutritional comorbidities that affect neurologically impaired child. Studies have reviewed the epidemiology, pathogenesis, assessment, and treatment of these disorders in neurologically impaired children.7,8

All children and adolescents have caloric requirements necessary for metabolism, growth, activity, fecal losses, and specific dynamic action of protein. The basic building blocks that provide these calories are protein, including essential amino acids (approximately 4 cal/g); fat, including essential fatty acids (approximately 9 cal/g); and carbohydrate (approximately 4 cal/g). In addition, it is important to consider the need of water, trace elements, and vitamins. To attain normal growth, it is necessary to meet both height and weight needs.

All nutrients must be ingested, retained, processed, absorbed, metabolized, and excreted; the net result of which should produce nutritional sufficiency. Ingestion and retention are dependent on proper mechanics. As children and adolescents are involved in various activities, there could be chances of them undergoing certain changes over time with regard to metabolic activity and growth needs, whether disabled or not. It is impossible to establish a single simple formula or equation to calculate all dietary needs.6 Children with neurological disabilities usually have progressive weight deficits due to fat loss, although muscle and visceral proteins are maintained. Some children demonstrate a lack of weight gain in the presence of linear growth, leading to a decreased body mass index (BMI), while some others have progressive muscle atrophy unresponsive to nutritional intervention because of their underlying disorder. Although neurologically impaired children are usually shorter and weigh less than unaffected children, a small proportion (8%–14%) may be overweight based on weight-for-height or triceps skin fold thickness criteria.9,10

Globally, the overall quality of the diet of school-age children and adolescents may be inadequate in large parts of the population. Families with a low socioeconomic status often cannot afford healthy diets,11 hence they have less access to micronutrient-rich foods such as fruits, vegetables, meat, fish, and dairy.12 In addition, school-age children may have an independent eating pattern;13 this can include more out-of-home food consumption without supervision, which is likely to result in increased intake of foods of low nutritional value, such as soft drinks and salty snacks in place of micronutrient-rich foods.14

School-age children and adolescents are in a stage of considerable physical and mental developments. The brain continues to mature until young adulthood, and cognitive functions, in particular the higher-order functions (reasoning, planning, abstract thinking, etc), develop and become more structured during this period.15 Therefore, it is crucial to meet the nutritional demands for optimal health, which can influence health and productivity in later stages of life. Undernutrition is also related to an increased risk of morbidity.16 Vitamin A and zinc deficiencies are associated with impaired immune function and higher susceptibility to infection and diarrhea.17 Deficiency of micronutrients such as iodine may affect mental development,18 leading to structural and functional impairments of the CNS.19 Undernourished or anemic children are less active and less likely to explore and interact with their environment, which can lead to suboptimal development.20 Interventions with micronutrients (multiple) have led to beneficial effects on linear growth,21 health,22 and cognitive development23 in school children.

As children are always active during this age, the pressure of maintaining the energy level of the kids solely depends on the parents. A wide range of contemporary and stylish health drinks in various flavors are available in the market with the aim to meet the changing consumer preferences and attract children.

HiOwna-Jr. is an innovative natural polyherbal formulation designed to promote general health and wellbeing of children, to support the optimum natural linear growth and development of children aged between 2 and 10 years, to additionally enhance immunity, and to help maintain adequate natural cognitive function.

**Aim**

To evaluate the clinical efficacy and safety of a polyherbal formulation
Materials and Methods

This was an open clinical trial conducted in children of known families. Local ethical committee approval was obtained before initiation of the study. Those who opted for treatment were informed of the voluntary nature of the trial and written consent was obtained from the parent or guardian. They were free to withdraw from the study.

Inclusion criteria

Fifty children, including both male and female, aged between 2 and 10 years and whose parent or guardian had given the consent to participate in the clinical trial were included in the study. Children suffering from any cardiac, hepatic, or renal failure or regularly on any treatment or concurrently taking medicines for any illness or any congenital anomaly such as cleft lip, etc, which hampers food intake, were excluded from the study. In addition, children with a strong intake, were excluded from the study. At each follow-up visit, information about intercurrent illness, therapeutic interventions, and concomitant medication/s were recorded. All the adverse events reported or observed by patients were also recorded with information about severity, date of onset, duration, and action taken regarding the study drug. The demographic data is presented in Table 1.

Relation of adverse events with study medication was predefined as "unrelated" (a reaction that does not follow a reasonable temporal sequence from the administration of the drug); "possible" (follows a known response pattern to the suspected drug, but could have been produced by the child’s clinical state or other modes of therapy administered to the child); and "probable" (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the child’s clinical state). Blood investigations were not performed for any children during the study procedure.

Primary endpoints: Improvement in general health, growth, and cognition.

Secondary endpoints: Short-term safety as assessed by incidence of adverse events, and compliance to the drug therapy.

Statistical analysis

All values are expressed, as compared to at entry, as mean ± standard deviation. Statistical analysis was carried out using repeated measures of analysis of variance (ANOVA) followed by Tukey’s multiple comparison test for parameters such as height, weight, and BMI. Functional parameters such as appetite, frequency of respiratory tract infection (RTI) and cognitive attention, memory, and concentration were evaluated by repeated measures of ANOVA using Friedman test followed by Dunnett’s multiple comparison test.
The minimum level of significance was fixed at $P < .05$. Statistical analysis was carried out using GraphPad Prism Software Version 4.00 for Windows (San Diego, California, USA).

### Table 1. Demographic Characteristics on Entry

<table>
<thead>
<tr>
<th>Number of subjects (n)</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>5.75 ± 2.62 (Min: 2 years; Max: 10 years)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>24:16</td>
</tr>
</tbody>
</table>

### Results

The effect of HiOwna-Jr. on parameters such as height, weight, and BMI are shown in Table 2. The mean height (centimeters) that was 110.6 ± 18.1 at entry improved to 111.3 ± 18.3 by the first month ($P < .001$) and further improved to 112.4 ± 18.5 by the second month ($P < .001$) after HiOwna-Jr. administration. Mean weight (kilogram) that was 18.70 ± 5.23 at entry improved to 19.12 ± 5.23 at the first month and further improved to 19.27 ± 5.23 by the second month after HiOwna-Jr. administration. Similarly, BMI (kilogram per meter square) also improved from 15.19 ± 1.85 at entry to 15.36 ± 1.96 at the first month ($P < .001$), and further to 15.19 ± 1.97 by the second month ($P < .001$) after HiOwna-Jr. administration.

The effects of HiOwna-Jr. on general health functional parameters such as appetite and frequency of RTI are shown in Table 3. The appetite score that was 1.53 ± 0.51 at entry improved to 2.53 ± 0.51 at the first month ($P < .001$ as compared to at-entry value) and further improved to 2.88 ± 0.33 by the second month ($P < .001$) with HiOwna-Jr. administration. Frequency of RTI that was 1.58 ± 1.01 at entry improved to 0.83 ± 0.75 at first month ($P < .001$ as compared to at-entry values) and further improved to 0.33 ± 0.47 with continued HiOwna-Jr. administration by the second month ($P < .001$). The effects of HiOwna-Jr. on cognitive parameters such as attention, memory, and concentration in children aged between 5 and 10 years are shown in Table 4. Attention score at entry was 1.52 ± 0.51 that further improved to 2.40 ± 0.58 ($P < .001$ as compared to at-entry values) at the first month and further improved to 2.92 ± 0.28 at the end of second month ($P < .001$) with HiOwna-Jr. administration. Similarly, memory score that was 1.60 ± 0.50 at entry improved to 2.40 ± 0.58 at first month ($P < .001$) and further improved to 2.96 ± 0.20 by the second month ($P < .001$) after HiOwna-Jr. administration. Concentration also improved from 1.56 ± 0.51 to 2.60 ± 0.50 at first month ($P < .001$ as compared to at-entry value) and further improved to 2.84 ± 0.37 at the second month ($P < .001$) after administration of HiOwna-Jr.

For all the parameters, the results indicated marked improvement in most children on HiOwna-Jr. treatment for a period of 2 months. No clinically significant adverse reactions were either reported or observed during the entire study period; and overall compliance to the treatment was excellent.

### Discussion

Low energy and protein intakes are the primary cause for poor growth and undernutrition due to protein energy deficiency and are associated with increased susceptibility to infectious diseases. Food fortification is a practical way to combine the benefits of energy repletion, adequate supply of fat and protein, and micronutrients to optimize the growth and development of children. Mental development of children can be affected by malnutrition directly through insufficient supply of essential micronutrients, leading to structural and functional impairments of the CNS. Micronutrient deficiencies can also have an indirect effect on mental and motor developments. Undernourished or anemic children are less active and less likely to explore and interact with their environment, which can lead to suboptimal development. Interventions with (multiple) micronutrients have led to beneficial effects on linear growth, health, and cognitive development in school children.

HiOwna-Jr. contains principal herbal ingredients such as Nartaka (Eleusine coracana), Marichia (Piper nigrum), Amalaki (Emblica officinalis), Mandukaparni (Centella asiatica), and other nutrients such as sucrose, peeyusha (colostrum), skimmed milk powder, corn solids (maltodextrin), pea protein powder, whey protein concentrate, minerals (calcium, phosphorous, iron, magnesium, zinc, chromium, selenium, molybdenum, and iodine), and vitamins (vitamin A, vitamin C, vitamin D, vitamin E, vitamin K, vitamin B1, vitamin B2, vitamin B6, vitamin B12, niacin, biotin, folic acid, and pantothenic acid). These ingredients contain nutritive, energy boosting, digestive, memory enhancing, and immunomodulatory properties that aids in providing a balanced nutrition and helps promote the overall health of children. Proteins, carbohydrates, and fats provide energy, promote growth and development, and regulate body functions. Vitamins and minerals have a beneficial effect on linear growth and health and cognitive development in school children. The beneficial effects of the health drink are discussed as follows:
Table 2. Effect of HiOwna-Jr. on Height, Weight, and BMI (n = 40)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At Entry</th>
<th>First Month</th>
<th>Second Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cms)</td>
<td>110.6 ± 18.1</td>
<td>111.3 ± 18.3</td>
<td>112.4 ± 18.5</td>
</tr>
<tr>
<td>Weight (kgs)</td>
<td>18.70 ± 5.23</td>
<td>19.12 ± 5.23</td>
<td>19.27 ± 5.23</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.19 ± 1.85</td>
<td>15.36 ± 1.96</td>
<td>15.19 ± 1.97</td>
</tr>
</tbody>
</table>

BMI, body mass index.

*As compared to at-entry values; †As compared to first month values.

Table 3. Effect of HiOwna-Jr. on Functional Parameters (n = 40)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At Entry</th>
<th>First Month</th>
<th>Second Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite</td>
<td>1.53 ± 0.51</td>
<td>2.53 ± 0.51</td>
<td>2.88 ± 0.33</td>
</tr>
<tr>
<td>Frequency of RTI</td>
<td>1.58 ± 1.01</td>
<td>0.83 ± 0.75</td>
<td>0.33 ± 0.47</td>
</tr>
</tbody>
</table>

RTI, respiratory tract infection.

*As compared to at-entry values; †As compared to first month values.

Table 4. Effect of HiOwna-Jr. on Cognitive Functional Parameters in Children Aged Between 5 and 10 Years (n = 25)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At Entry</th>
<th>First Month</th>
<th>Second Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>1.52 ± 0.51</td>
<td>2.40 ± 0.58</td>
<td>2.92 ± 0.28</td>
</tr>
<tr>
<td>Memory</td>
<td>1.60 ± 0.50</td>
<td>2.40 ± 0.58</td>
<td>2.96 ± 0.20</td>
</tr>
<tr>
<td></td>
<td>1.56 ± 0.51</td>
<td>2.60 ± 0.50</td>
<td>2.84 ± 0.37</td>
</tr>
</tbody>
</table>

*Significance as compared to at-entry values.

Enhancement of nutrient absorption and gastroprotective effects

*P* nigra*, a rich source of piperine, was found to increase the secretion of bile in experimental studies. This suggests that it aids in the digestion and absorption of dietary fats. It has also been found to protect against the gastric damage caused by gastric irritant agents that might be related to the inhibition of gastric motor activity and the stimulation of prostaglandin synthesis. Dietary piperine, by favorably stimulating the pancreatic digestive enzymes, not only enhances the digestive capacity and significantly reduces the GI food transit time, but also increases bioavailability of many phytochemicals by its inhibitory influence on enzymatic drug biotransforming reactions in the liver. This property is also partly attributed to increased absorption due to its effect on the ultrastructure of intestinal brush border.

Immunomodulatory activity

An experimental study showed that *E. officinalis* or amla was effective against the cytotoxic effects of chromium (Cr)-induced oxidative damage of murine macrophages, enhanced cell survival, decreased free radical production, and led higher antioxidant levels similar to that of control cells. Further, it was observed that Cr treatment decreased phagocytosis and γ-interferon (γ-IFN), while *E. officinalis* inhibited Cr-induced immunosuppression and significantly restored both phagocytosis and γ-IFN production by macrophages. These findings indicate its cytoprotective and immunomodulatory properties. In another in-vitro study, *E. officinalis* relieved the immunosuppressive effects of Cr on lymphocyte proliferation and even restored the interleukin (IL)-2 and γ-IFN

Nutritive and health-promoting

*E. coracana* is known for its nutritive and strength enhancing properties. It is rich in protein, iron, calcium (higher than all cereals), phosphorus, fiber, and vitamins. Ragi contains the best quality protein, including essential amino acids, vitamin A, vitamin B, and phosphorus. It also provides highest level of calcium, antioxidants, and phytochemicals, which makes it easily and slowly digestible. Malting of finger millet improves digestibility, sensory, and nutritional quality as well as pronounced effect in lowering antinutrients. Thus, it is a good source of diet for growing children. Bovine colostrum is an excellent source of nutrition that helps in promoting body growth. Proteins, carbohydrates, and fat are required for growth, maintenance, and highly specialized functions of the body as well as energy sources. Vitamins and minerals are known for their health-promoting functions in the body.
productions considerably. An experimental study conducted on mice demonstrated that the aqueous extract of *E. officinalis* was very effective in reducing cyclophosphamide-induced suppression of humoral immunity. Bovine colostrum had the ability to increase IgA, indicating its potential to enhance human special immune response.

Promoting mental health

A double-blind clinical trial on *C. asiatica* observed a significant improvement in the general mental ability of children who were mentally retarded, after 3 and 6 months of administration. Significant improvement was also found in the overall general adjustment, attention, and concentration after 6 months. Another study concluded that *C. asiatica* leaf extract had a neuronal dendritic growth stimulating property; hence, the extract could be used to enhance neuronal dendrites in stress, neurodegenerative, and memory disorders. These studies indicate that *C. asiatica* improves the memory and learning ability. Micronutrients such as vitamins and minerals, when delivered through either supplements or fortified foods, were found to have a positive effect on reasoning ability and academic performance in school children.

Conclusion

This clinical study clearly demonstrates that Hi Owna-Jr., a polyherbal natural health drink supplement, when given in addition to regular diet showed a trend toward improvement in the growth as determined by height, weight, and BMI, including general health as determined by reduction of RTI frequency and improvement in the appetite of children aged between 2 and 10 years. The improvement in the growth corresponded to the normal natural growth in children, which implies that Hi Owna-Jr. helps in the normal natural linear growth of children. Cognition parameters such as attention, memory, and concentration evaluated in school-going children aged between 5 and 10 years also showed beneficial results. All the children preferred the taste and flavor, hence there were no dropouts. Overall compliance to the study was good. No adverse effects were either reported or observed during the clinical study. It was safe without any adverse effects for short-term and long-term uses. Therefore, it can be concluded that Hi Owna-Jr., given in addition to regular balanced diet, helps maintain adequate natural linear growth, enhance immunity, and favorably, modify cognition in children.

References

Evaluation of Efficacy and Safety of Bresol (HK-07) Tablets in Children with Upper and Lower Respiratory Tract Allergic Diseases

Sengupta K, Kolhapure SA


Abstract

The present study was an open, noncomparative phase III clinical trial that included 105 children within the age group of 3 to 12 years, who presented with symptoms of rhinitis or bronchitis; and were treated with Bresol. At initial visit, a detailed medical history was obtained by interviewing the child and parent/guardian followed by thorough clinical examination, with special emphasis on the respiratory system. All children were followed fortnightly for a period of 3 months and investigated by hematological and biochemical tests along with peak expiratory flow rate at the end of the study period. The predefined primary endpoints were rapid symptomatic control and clinical, biochemical, and hematological improvements.

Of the 105 enrolled children, 4 children were lost to follow-up, while the data of the remaining 101 children were analyzed. There was a highly significant reduction in mean scores for sneezing, nasal congestion, itching of the eyes and nose, postnasal drip, rhinorrhea, watery eyes, and total rhinitis symptom score at the end of the study. In addition, a significant reduction was also observed in mean scores of chest tightness, daily asthmatic symptoms, wheezing, shortness of breath, cough, sputum production, and total asthma symptom score at the end of the study. There were no clinically significant reported or observed adverse events.

Therefore, it can be concluded that Bresol (HK-07) tablets are clinically effective and safe in children suffering from allergic rhinitis, allergic bronchitis, or asthmatic bronchitis.

Introduction

Increasing prevalence of upper and lower respiratory tract allergic diseases (rhinitis, bronchitis, and asthma) is a serious health issue affecting a major chunk of global population, as these diseases are responsible for significant morbidity and severe economic impact. This impact is even more severe in children due to associated long-term compromises in the quality of life.

Various epidemiological studies have identified the causes for this increase in the prevalence of upper and lower respiratory tract allergic diseases. The postulated reasons are as follows: increasing environmental pollution and increased predisposition of individuals producing excessive immunoglobulin E (IgE), through a major change in the gene pool, leading to increased expression of these diseases. Decreasing incidence of early childhood infections directs the immune system of the infants’ toward allergy rather than protection against infection. Other important causes include changing lifestyles and an increasing awareness of these disorders.
The available treatment options for upper and lower respiratory tract allergic diseases have major limitations due to low efficacy, associated adverse events, and compliance issues. Antihistamines, sympathomimetics, and xanthine derivatives are commonly used as the first-line treatment for symptomatic management, but they do not prevent recurrent episodes. Use of glucocorticosteroids and anticholinergics is questionable due to long-term adverse effects. Prophylactic use of mast cell stabilizers has the disadvantage of frequent administration. Decongestant drugs are effective in the treatment of nasal obstruction, but they do not improve other symptoms of rhinitis and have high incidence of adverse effects. Studies using leukotriene receptor antagonists as a sole therapy in these allergic diseases have proved to be disappointing.

Bresol (HK-07) tablet is a polyherbal formulation indicated for the management of upper and lower respiratory tract allergic diseases. It contains extracts of Curcuma longa, Ocimum sanctum, Adhatoda vasica, Trikatu, Triphala, Embelia ribes, Cyperus rotundus, Cinnamomum zeylanicum, Elettaria cardamomum, Cinnamomum tamala, and Mesua ferrea.

This study was conducted to evaluate the efficacy and safety (for short-term and long-term) of Bresol (HK-07) tablets in upper and lower respiratory tract allergic diseases.

**Aim**

This study was planned to evaluate the clinical efficacy and safety of Bresol (HK-07) tablets in children (within the age group of 3–12 years) suffering from allergic rhinitis, allergic bronchitis, or asthmatic bronchitis.

**Study design**

The study was an open, noncomparative, phase III clinical trial conducted at the Bai Jerbai Wadia Hospital for Children, Mumbai, from July to October 2002, as per the ethical guidelines of Declaration of Helsinki. The study protocol, case report forms (CRFs), regulatory clearance documents, product-related information, and informed consent form (in English, Hindi, and Marathi) were submitted to the Institutional Ethics Committee and were approved by the same.

**Materials and Methods**

**Inclusion criteria**

One hundred and five children within the age group of 3 to 12 years presented with symptoms of rhinitis (sneezing, nasal congestion, itching of the eyes and nose, postnasal drip, rhinorrhea, and watery eyes) or bronchitis (allergic and asthmatic symptoms such as chest tightness, wheezing, productive cough, and nocturnal asthma) were included in the study.

**Exclusion criteria**

Severely malnourished children and children with severe systemic illness were excluded from the study.

**Study procedures**

The children and/or the parents (or guardian) of the children were informed about the study drug, its effects, duration of the study, their responsibilities, importance of compliance, patient’s rights, ethical aspects, and overall plan of the study. Informed consent was obtained from parents/guardians of all included children and a witness, who was unrelated to the clinical trial, attested the same.

At initial visit, a detailed medical history was obtained by interviewing the child and parent/guardian followed by a thorough clinical examination, with special emphasis on the respiratory system. The details of the clinical examination were recorded in the CRF. All children were subdivided into 3 subgroups: Group A included all children with allergic rhinitis, group B included all children with allergic bronchitis, and group C included all children with asthmatic bronchitis. All children were investigated by hematological and biochemical tests (hemoglobin [Hb], white blood cell [WBC] count, differential leukocyte count [DLC] count, erythrocyte sedimentation rate [ESR], serum creatinine [SC], serum glutamic pyruvic transaminase [SGPT], serum bilirubin [SB], and peak expiratory flow rate [PEFR] recording was done) to determine the functional lung capacity.

Each child was advised to consume Bresol (HK-07) tablets in the following dosage schedule: for children suffering from allergic rhinitis and allergic bronchitis the recommended dosage was 1 tablet, twice daily, for 2 weeks, while for children suffering from asthmatic bronchitis the recommended dosage was 1 tablet, twice daily, for 12 weeks.

**Follow-up and monitoring**

All children were followed fortnightly for a period of 3 months. At each follow-up visit, clinical examination was done for evaluating the following parameters: symptomatic improvement of rhinitis (sneezing, nasal congestion, itching of the eyes and nose, postnasal drip, rhinorrhea, and watery eyes), total rhinitis symptom score (0-nil, 1-mild, 2-moderate, 3-severe), symptomatic improvement of asthmatic bronchitis and allergic bronchitis (chest tightness, wheezing, cough, sputum production, and nocturnal asthma), total asthmatic symptoms score.
(0-nil, 1-mild, 2-moderate, 3-severe), PEFR and reduction in daily usage of number of bronchodilator inhalations. All children were investigated by hematological and biochemical tests (Hb, WBC, DLC, ESR, SC, SGPT, and SB) along with PEFR at the end of the study period.

Adverse events
All adverse events, either reported or observed by patients, were recorded in CRF with information on severity, onset, duration, and action taken as regards the study drug. Relation of adverse events with study medication was predefined as “Unrelated” (a reaction that does not follow a reasonable temporal sequence from the time of administration of the drug), “Possible” (a reaction that follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and “Probable” (a reaction that follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study if they experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Noncompliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, but reasons for noncompliance were noted.

Primary and secondary endpoints
The predefined primary endpoints were rapid symptomatic control as well as clinical, biochemical, and hematological improvements. The predefined secondary endpoints were incidences of short-term and long-term adverse events and overall compliance to the drug treatment.

Statistical analysis
Statistical analysis was carried out according to intention-to-treat principles. Changes in various parameters from baseline values and values after the 2, 4, 6, and 12 weeks were analyzed by “Repeated Measures ANOVA Test,” followed by “Bonferroni’s Multiple Comparison Test.” The changes in the values, before the initiation of study and at the end of the study, were analyzed by “Paired t test.” The minimum level of significance was fixed at 99% confidence limit, and a 2-sided P value of < .0001 was considered significant.

Results
Of the 105 enrolled children, 4 children were lost to follow-up, while the data of the remaining 101 children were analyzed. There were 83 (82%) children aged between 3 and 6 years, 10 (10%) children aged between 6 and 9 years, and 8 (08%) children aged between 9 and 12 years. In addition, a significant male preponderance was observed (63 males and 42 females). Of the total 101 children, 39 (38%) were classified under group A, 28 (28%) were classified under group B, and 34 (34%) were classified under group C (Table 1).

There was a highly significant reduction in mean scores for symptomatic evaluation of sneezing, coughing, lacrimation, and rhinorrhea in group A (P < 0.0001), group B (P < 0.0001), and group C (P = 0.0001) compared to baseline (Figure 1).

The reduction in symptom score (0-nil, 1-mild, 2-moderate, 3-severe) of total rhinitis was observed in group A (P < 0.0001), group B (P < 0.0001), and group C (P = 0.0001) compared to baseline (Figure 2).

The reduction in symptom score (0-nil, 1-mild, 2-moderate, 3-severe) of asthma was observed in group A (P < 0.0001), group B (P < 0.0001), and group C (P = 0.0001) compared to baseline (Figure 3).

All adverse events, either reported or observed by patients, were recorded in CRF with information on severity, onset, duration, and action taken as regards the study drug. Relation of adverse events with study medication was predefined as “Unrelated” (a reaction that does not follow a reasonable temporal sequence from the time of administration of the drug), “Possible” (a reaction that follows a known response pattern to the suspected drug), and “Probable” (a reaction that follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

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The reduction in symptom score (0-nil, 1-mild, 2-moderate, 3-severe) of asthma was observed in group A (P < 0.0001), group B (P < 0.0001), and group C (P = 0.0001) compared to baseline (Figure 3).

All adverse events, either reported or observed by patients, were recorded in CRF with information on severity, onset, duration, and action taken as regards the study drug. Relation of adverse events with study medication was predefined as “Unrelated” (a reaction that does not follow a reasonable temporal sequence from the time of administration of the drug), “Possible” (a reaction that follows a known response pattern to the suspected drug), and “Probable” (a reaction that follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study if they experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Noncompliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, but reasons for noncompliance were noted.

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Statistical analysis
Statistical analysis was carried out according to intention-to-treat principles. Changes in various parameters from baseline values and values after the 2, 4, 6, and 12 weeks were analyzed by “Repeated Measures ANOVA Test,” followed by “Bonferroni’s Multiple Comparison Test.” The changes in the values, before the initiation of study and at the end of the study, were analyzed by “Paired t test.” The minimum level of significance was fixed at 99% confidence limit, and a 2-sided P value of < .0001 was considered significant.

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The reduction in symptom score (0-nil, 1-mild, 2-moderate, 3-severe) of asthma was observed in group A (P < 0.0001), group B (P < 0.0001), and group C (P = 0.0001) compared to baseline (Figure 3).
### Table 1. Age-wise and Disease-wise (Group) Distributions of Children

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of Children</th>
<th>Group</th>
<th>No. of Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–6</td>
<td>83</td>
<td>Group A</td>
<td>39</td>
</tr>
<tr>
<td>6–9</td>
<td>10</td>
<td>Group B</td>
<td>28</td>
</tr>
<tr>
<td>9–12</td>
<td>8</td>
<td>Group C</td>
<td>34</td>
</tr>
</tbody>
</table>

### Table 2. Reduction in Mean Symptom Scores for Sneezing, Nasal Congestion, Itching of the Eyes, Itching of the Nose, Postnasal Drip, Rhinorrhea, Watery Eyes, and Total Rhinitis (Repeated Measures ANOVA with Bonferroni Multiple Comparison Test Statistics)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline</th>
<th>Second Week</th>
<th>Fourth Week</th>
<th>Sixth Week</th>
<th>Twelfth Week</th>
<th>F</th>
<th>R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sneezing</td>
<td>0.5243</td>
<td>0.09709</td>
<td>0.07767</td>
<td>0.07767</td>
<td>0.05825</td>
<td>69.35</td>
<td>0.4047</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SD</td>
<td>0.5019</td>
<td>0.2975</td>
<td>0.2690</td>
<td>0.2690</td>
<td>0.2354</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.04945</td>
<td>0.02932</td>
<td>0.02650</td>
<td>0.02650</td>
<td>0.02319</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>0.6117</td>
<td>0.08738</td>
<td>0.04854</td>
<td>0.04854</td>
<td>0.009709</td>
<td>92.48</td>
<td>0.4755</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SD</td>
<td>0.4898</td>
<td>0.2838</td>
<td>0.2160</td>
<td>0.2160</td>
<td>0.09853</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.04826</td>
<td>0.02796</td>
<td>0.02128</td>
<td>0.02128</td>
<td>0.009709</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching of the eyes</td>
<td>0.2816</td>
<td>0.01942</td>
<td>0.01942</td>
<td>0.009709</td>
<td>0.009709</td>
<td>31.07</td>
<td>0.2335</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SD</td>
<td>0.4520</td>
<td>0.1387</td>
<td>0.09853</td>
<td>0.09853</td>
<td>0.009709</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.04453</td>
<td>0.01366</td>
<td>0.01366</td>
<td>0.09853</td>
<td>0.009709</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching of the nose</td>
<td>0.2524</td>
<td>0.01942</td>
<td>0.01942</td>
<td>0.009709</td>
<td>0.009709</td>
<td>30.55</td>
<td>0.2305</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SD</td>
<td>0.4365</td>
<td>0.1387</td>
<td>0.09853</td>
<td>0.09853</td>
<td>0.009709</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.04301</td>
<td>0.01366</td>
<td>0.01366</td>
<td>0.09853</td>
<td>0.009709</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postnasal drip</td>
<td>0.2913</td>
<td>0.009709</td>
<td>0.009709</td>
<td>0.009709</td>
<td>0.009709</td>
<td>36.73</td>
<td>0.2648</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SD</td>
<td>0.4566</td>
<td>0.09853</td>
<td>0.09853</td>
<td>0.09853</td>
<td>0.09853</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.04499</td>
<td>0.009709</td>
<td>0.009709</td>
<td>0.009709</td>
<td>0.009709</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>0.6602</td>
<td>0.1456</td>
<td>0.09709</td>
<td>0.06796</td>
<td>0.06796</td>
<td>90.23</td>
<td>0.4694</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SD</td>
<td>0.4760</td>
<td>0.3545</td>
<td>0.2975</td>
<td>0.2529</td>
<td>0.09853</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.04690</td>
<td>0.03493</td>
<td>0.02932</td>
<td>0.02492</td>
<td>0.009709</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watery eyes</td>
<td>0.5922</td>
<td>0.1165</td>
<td>0.09709</td>
<td>0.08738</td>
<td>0.009709</td>
<td>74.74</td>
<td>0.4229</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SD</td>
<td>0.4938</td>
<td>0.3224</td>
<td>0.2975</td>
<td>0.2838</td>
<td>0.09853</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.04866</td>
<td>0.03177</td>
<td>0.02932</td>
<td>0.02796</td>
<td>0.009709</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total rhinitis score</td>
<td>1.583</td>
<td>1.029</td>
<td>0.2913</td>
<td>0.1553</td>
<td>0.01942</td>
<td>245.8</td>
<td>0.7067</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SD</td>
<td>0.7862</td>
<td>0.4528</td>
<td>0.4776</td>
<td>0.3640</td>
<td>0.1387</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.07747</td>
<td>0.04462</td>
<td>0.04706</td>
<td>0.03587</td>
<td>0.01366</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance; SD, standard deviation; SEM, standard error of the mean.

Discussion

The natural history of upper and lower respiratory tract allergic diseases is complex and is influenced by multifactorial pathological processes. Exposure to an allergen activates CD4+ T lymphocytes leading to release of cytokines (interleukin-3 [IL-3], IL-4, and IL-5), increased IgE production, and infiltration of specific cells (plasma cells, mast cells, and eosinophils). With repeated allergen challenge, the amount of allergen necessary to trigger an allergic response decreases (“priming effect”). This IgE-mediated immune response to a specific allergen induces inflammation (allergic inflammation).
Table 3. Reduction in Mean Symptom Scores for Chest Tightness, Daily Asthmatic Symptoms, Wheezing, Shortness of Breath, Cough, Sputum Production, and Total Asthma Symptoms (Repeated Measures ANOVA with Bonferroni Multiple Comparison Test Statistics)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>Second Week</th>
<th>Fourth Week</th>
<th>Sixth Week</th>
<th>Twelfth Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest tightness</td>
<td>Mean</td>
<td>0.2136</td>
<td>0.009709</td>
<td>0.009709</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.4350</td>
<td>0.09853</td>
<td>0.09853</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>0.04286</td>
<td>0.009709</td>
<td>0.009709</td>
<td>0.0</td>
</tr>
<tr>
<td>F = 22.95, R² = 0.1837, P &lt; .0001, Significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily asthmatic symptoms</td>
<td>Mean</td>
<td>0.2524</td>
<td>0.04854</td>
<td>0.03883</td>
<td>0.02913</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.5186</td>
<td>0.3248</td>
<td>0.3107</td>
<td>0.2956</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>0.05110</td>
<td>0.03200</td>
<td>0.03061</td>
<td>0.02913</td>
</tr>
<tr>
<td>F = 18.23, R² = 0.1516, P &lt; .0001, Significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td>Mean</td>
<td>0.3398</td>
<td>0.01942</td>
<td>0.01942</td>
<td>0.009709</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.4760</td>
<td>0.1387</td>
<td>0.1387</td>
<td>0.09853</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>0.04690</td>
<td>0.01366</td>
<td>0.01366</td>
<td>0.009709</td>
</tr>
<tr>
<td>F = 46.35, R² = 0.3125, P &lt; .0001, Significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Mean</td>
<td>0.3204</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.4689</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>0.04620</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>F = 48.09, R² = 0.3204, P &lt; .0001, Significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>Mean</td>
<td>0.6117</td>
<td>0.07767</td>
<td>0.05825</td>
<td>0.009709</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.4898</td>
<td>0.2690</td>
<td>0.2354</td>
<td>0.09853</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>0.04826</td>
<td>0.02650</td>
<td>0.02319</td>
<td>0.009709</td>
</tr>
<tr>
<td>F = 109.1, R² = 0.5168, P &lt; .0001, Significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum production</td>
<td>Mean</td>
<td>0.3010</td>
<td>0.07767</td>
<td>0.06796</td>
<td>0.02913</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.4817</td>
<td>0.3032</td>
<td>0.2529</td>
<td>0.1690</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>0.04747</td>
<td>0.02988</td>
<td>0.02492</td>
<td>0.01665</td>
</tr>
<tr>
<td>F = 26.48, R² = 0.2061, P &lt; .0001, Significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total asthma symptom score</td>
<td>Mean</td>
<td>1.097</td>
<td>0.5146</td>
<td>0.3107</td>
<td>0.1569</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.249</td>
<td>0.7652</td>
<td>0.6108</td>
<td>0.4613</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>0.1230</td>
<td>0.07540</td>
<td>0.06019</td>
<td>0.04567</td>
</tr>
<tr>
<td>F = 54.16, R² = 0.3468, P &lt; .0001, Significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance; SD, standard deviation; SEM, standard error of the mean.

and is responsible for the clinical manifestations of these allergic diseases. There are 2 distinct phases of allergic rhinitis that are divided as follows: the immediate or early-phase response (within minutes after allergen exposure) and the late-phase response (4–8 h after allergen exposure).5,10

In the early-phase response, there is increase in the titer of IgE in the epithelium and IgE binds to its receptor (Fc [ε] RI) on tissue mast cells that triggers the mast cell degranulation.11 Degranulation of mast cells releases chemokines such as histamine, tryptase, chymase, kininogenase (which generates bradykinin), heparin, prostaglandin D2, tumor necrosis factor (TNF), leukotriene (LT)-C4, LT-D4, and LT-E4. Bradykinin causes vasodilation and increases vascular permeability, leading to mucosal edema that is clinically manifested as watery rhinorrhea.12 Simultaneously, the binding of IgE to receptor (Fc [ε] RI) on basophils results in basophil degranulation, releasing various inflammatory chemokines, lipid mediators, and cytokines.13 Concurrent secretion of mucoglycoconjugates and antimicrobial compounds by mucosal glands causes vasodilation leading to sinusoidal filling that is clinically
Table 4. Increased Levels of WBC, Eosinophils, Polymorphs, Lymphocytes, and ESR (Paired t Test)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Twelfth Week</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC (cells/cumm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>12,922</td>
<td>10,330</td>
</tr>
<tr>
<td>SD</td>
<td>3128</td>
<td>1932</td>
</tr>
<tr>
<td>SEM</td>
<td>391.0</td>
<td>241.6</td>
</tr>
<tr>
<td><strong>Eosinophils (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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</tr>
<tr>
<td>SD</td>
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<td>0.8817</td>
</tr>
<tr>
<td>SEM</td>
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<td>0.1430</td>
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<tr>
<td><strong>Polymorphs (%)</strong></td>
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<tr>
<td>Mean</td>
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<td>39.45</td>
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<tr>
<td>SD</td>
<td>11.84</td>
<td>12.22</td>
</tr>
<tr>
<td>SEM</td>
<td>1.202</td>
<td>1.247</td>
</tr>
<tr>
<td><strong>Lymphocytes (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>51.78</td>
<td>45.99</td>
</tr>
<tr>
<td>SD</td>
<td>13.28</td>
<td>12.87</td>
</tr>
<tr>
<td>SEM</td>
<td>1.348</td>
<td>1.307</td>
</tr>
<tr>
<td><strong>ESR (mm/h)</strong></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>16.45</td>
<td>10.37</td>
</tr>
<tr>
<td>SD</td>
<td>7.529</td>
<td>5.967</td>
</tr>
<tr>
<td>SEM</td>
<td>0.8935</td>
<td>0.7082</td>
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**r = 9.281, P < .0001, Significant**

Table 5. Global Evaluation of Treatment and Reduction in Severity of Symptoms (Repeated Measures ANOVA with Bonferroni Multiple Comparison Test Statistics)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Second Week</th>
<th>Fourth Week</th>
<th>Sixth Week</th>
<th>Twelfth Week</th>
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<tr>
<td><strong>Global evaluation of treatment</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>0.1553</td>
<td>0.2330</td>
<td>0.3495</td>
<td>0.5340</td>
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<tr>
<td>SD</td>
<td>0.5379</td>
<td>0.5637</td>
<td>0.6524</td>
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</tr>
<tr>
<td>SEM</td>
<td>0.05300</td>
<td>0.05554</td>
<td>0.06429</td>
<td>0.07534</td>
<td>0.1252</td>
</tr>
<tr>
<td><strong>Reduction in severity of symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>1.388</td>
<td>0.5980</td>
<td>0.3107</td>
<td>0.1845</td>
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<td>SD</td>
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<td>0.7347</td>
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<tr>
<td>SEM</td>
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<td>0.07275</td>
<td>0.05858</td>
<td>0.04729</td>
<td>0.01913</td>
</tr>
</tbody>
</table>

**F = 43.31, R² = 0.2980, P < .0001, Significant**

**F = 90.10, R² = 0.4690, P < .0001, Significant**

ANOVA, analysis of variance; SD, standard deviation; SEM, standard error of the mean.

manifested as nasal congestion. These chemomediators also stimulate sensory nerves that produce itching of the nose and eyes; along with sneezing induced by systemic reflexes.5

In the late-phase response, the chemomediators act on endothelial cells and promote the expression of adhesion molecules (vascular cell adhesion molecule and E-selectin) that facilitate the adhesion of circulating leukocytes to the endothelial cells. IL-5 promotes the mucosal infiltration and activation of eosinophils, neutrophils, basophils, T-lymphocytes, and macrophages. After activation, these cells release inflammatory chemomediators that reactivate many of the proinflammatory reactions of the early-phase response.5,14

Eosinophils release specific proteins (major basic protein, eosinophil cationic protein), LT-C4, platelet-activating factor, TNF, transforming growth factor-β, and IL-5, all of which cause epithelial damage.15 T-helper 2 lymphocytes release cytokines (IL-3, IL-4, IL-5) that promote IgE production, eosinophil chemoattraction, eosinophil survival, and mast cell recruitment.16 IL-5 stimulates CD34+ progenitor cells in the bone marrow to differentiate into eosinophils17 and plays a central role in eosinophil mobilization from the bone marrow.18 Once released from the bone marrow, eosinophils travel through the bloodstream and migrate into tissue sites where they recognize adhesion counterreceptors.19 In addition, eosinophils have both shared and distinct adhesion pathways with respect to neutrophils.20 IL-1 and TNF, released after allergen challenge, are crucial in the induction of endothelial-cell adhesiveness, which is a prerequisite for the recruitment of circulating eosinophils.21

Recently, the role of some of the newly identified chemomediators has been
highlighted in the pathophysiology of allergic respiratory tract disorders.5 Substance P is known to trigger smooth muscle constriction and acute inflammation,22 whereas nerve growth factor (NGF) enhances the production of substance P by neurons.23 NGF is a neurotropin produced not only by neuronal cells but also by immune cells (mast cells, macrophages, T-cells, and B-cells). NGF acts as a mediator in the interactions between immune and nerve cells.24 Local NGF upregulation along with amplification of the Th2 immune response was shown to contribute to the development of airway hyperreactivity.25 Oh et al demonstrated the important role of inducible nitric oxide synthase (iNOS) in allergic inflammation.26 Benson et al reported an increase in the expression of vascular endothelial growth factor-A in allergic patients.27 Chemokines (chemotactic cytokines) mediate cell migration and these molecules have been shown to be important leukocyte chemical attractants to sites of inflammation and infection. Banwell et al investigated the role of Th2-expressed CCCR4 and observed allergen-specific CCCR4 positivity of Th2 cells.28 Chemokine eotaxin-1 plays an important role in cell recruitment, inflammation, and tissue damage along with Th2 cytokines (IL-13 and IL-4).29 Thymus and activation-regulated chemokine (TARC) are produced by peripheral blood mononuclear cells, monocytes, macrophages, thymic cells, dendritic cells, endothelial cells, and bronchial epithelial cells; and TARC induces integrin-dependent adhesion of memory T-cells (CCCR4 serves as a receptor for TARC).31,32 Scavuzzo et al reported important anti-inflammatory and counterregulatory actions of IL-6 and IL-10 on the pathogenesis of allergic rhinitis.32 Endothelin-1 is known to play a role in airway smooth muscle contraction, bronchial obstruction, airway wall edema, and airway remodeling. It also possesses proinflammatory properties and plays a role in late-phase response. Antagonization of endothelin-1 has been shown to clearly inhibit airway eosinophilia and the development of bronchial hyperreactivity.5,33

This study observed an excellent and rapid symptomatic control, which was evident by a highly significant reduction in the mean scores for sneezing, nasal congestion, itching of the eyes and nose, postnasal drip, rhinorrhea, watery eyes, and total rhinitis symptom score at the end of the study. A significant reduction was also observed in mean scores for symptomatic evaluation of chest tightness, daily asthmatic symptoms, wheezing, shortness of breath, cough, sputum production, and total asthma symptom score at the end of the study. In addition, there was a significant improvement in the mean scores of PEFR. The pathological changes in the levels of hematological and biochemical parameters noted at the time of enrollment were renormalized without any clinically significant adverse events. This excellent outcome might be due to the synergistic actions of the ingredients present in Bresol (HK-07) tablets.

**Components of Bresol (HK-07) tablets**

Curcumin was reported to have anti-allergic property, as tested in an in-vitro model of airway hyperresponsiveness.34 In various animal and human studies, curcumin-I, curcumin-II, and curcumin-III (components of C. longa)55 have been shown to inhibit a number of molecules involved in inflammation (phospholipase, lipoperoxidase [LO], cyclooxygenase-1 [COX-1] and COX-2, LT, thromboxane [TX], prostaglandin [PG], nitric oxide [NO], collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1, interferon [IFN]-inducible protein, TNF, and IL-12).36,37 Inhibition of LO-1 was shown to be due to the ability of curcumin to bind with phosphatidylcholine micelles.38 Enhanced suppression of COX-2 expression was observed due to extracellular signal-regulated kinase activity and nuclear factor-kappaB (NF-κB) activation inhibition, which might be the molecular mechanisms of action.39 Kang et al observed that curcumin significantly inhibited production of IL-12, reduced the induction of IFN-γ, IL-4 in CD4+ T-cells by macrophages, leading to the inhibition of Th1 cytokine profile (IFN-γ and IL-4 production) in CD4+ T-cells.40 Curcumin is a potent antioxidant; it inhibits Ca2+ entry and protein kinase C activity.41 It also has an immunostimulatory activity and hence increases the circulating antibody titer, plaque forming cells, alpha-esterase positive cells, and phagocytosis.

The active ingredients of Zingiber officinale are gingerols and dihydroxyflavanoids, both of which are potent inhibitors of prostaglandin biosynthesizing enzyme (PG synthetase); and the structures of these compounds indicate that the inhibitors are also active against arachidonate 5 LO (an enzyme of leukotriene biosynthesis). Umeda et al recorded that Z. officinale inhibited biotransformation of AA, comparable to indomethacin.43 The other ingredients of Z. officinale include oleoresins (8)-paradol, (8)-shogaol that have inhibitory effects on COX-2 enzymes44 and the mechanism of action was hypothesized by the
attenuation of COX-1/TX synthase enzymatic activity. COX-1 and COX-2 (regulated by the eukaryotic transcription factor NF-κB) have been recognized as molecular targets for actions of *Z officinale*, and [6]-gingerol acts by interfering with intracellular signaling cascades, those involving NF-κB and mitogen-activated protein kinases. Thomson et al documented significant inhibitory effects of *Z officinale* on PG-E2 production. Ahmed et al observed that the antioxidant effect of *Z officinale* was comparable to ascorbic acid as demonstrated by lowered lipid peroxidation, while maintaining the activities of other antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase). [6]-Gingerol was found to be a potent inhibitor of iNOS and also an effective protector against peroxynitrite-mediated damage. Wilasrusmee et al reported immunosuppressive effects of *Z officinale* in vitro as evident by the decreased responsiveness in lymphocyte culture. The extract of *Z officinale* was shown to raise the thymus index, spleen index, phagocytosis, the rate of α-naphthyl acetate esterase+, and the titer of IgM, which indicates immunostimulation.

The principle anti-inflammatory ingredients of *Piper longum* are dihydrokawain, yangonin, and methysticin. Choudhary et al documented that *P longum* inhibits the lipid peroxidation process effectively by its ability to scavenge free radicals involved in the initiation and propagation steps. Chiou et al observed that *P longum* retards the recruitment of macrophages and suppresses cytokine production. Hashimoto et al isolated kava pyrones from *P longum* and recorded the inhibition of TNF release.

The principle ingredients of *Emblica officinalis* are tannoids (emblicanin-A and emblicanin-B, punigluconin, and pedunculagin). In addition to the antitussive activity, it was observed that *E officinalis* has anti-inflammatory, antispasmodic, and antioxidant efficacies as well as it reduces the mucus secretion in the airways. Khanom et al identified the strong superoxide-scavenging and prolyl endopeptidase inhibitory activity of *E officinalis*. Sai Ram et al observed that *E officinalis* significantly inhibited free radical production, restored the antioxidant status, inhibited apoptosis and DNA fragmentation, relieved the immunosuppressive effects on lymphocyte proliferation, and even restored the IL-2 and γ-IFN production. In another study, it was observed that *E officinalis* acts as an immunomodulator and decreases the induction of iNOS. Yet another study reported that *E officinalis* enhanced cell survival, decreased free radical production, ensured higher antioxidant levels, inhibited induced immunosuppression, and restored both phagocytosis and γ-IFN production by macrophages.

Tasaduq et al demonstrated potent anti-oxidative activity of *Terminalia belerica*. *T belerica* inhibited lipid peroxide formation by scavenging hydroxyl and superoxide radicals in vitro. Saleem et al observed the antioxidant potential of *T belerica* (stronger than alphatocopherol), which was attributed to hydroxybenzoic acid and hydroxycinnamic acid derivatives, flavonol aglycones and their glycosides.

Godhwani et al documented that *O sanctum* has an immunostimulatory effect on the humoral immunologic response (an increase in antibody titer) as well as on the cellular immunologic response (E-rosette formation and lymphocytosis).

**Bresol Ameliorates Experimental Chronic Obstructive Pulmonary Disease in Rats**

Rafq M, et al

*Ind J Pharm.* 2011;43(suppl 1):S190.

The study objective was to investigate the beneficial effect of Bresol in an experimental model of cigarette smoke (CS)-induced chronic obstructive pulmonary disease (COPD) in rats. Male Wistar rats weighing 200 to 250 g were randomized based on body weight into 4 groups (n = 10). All the animals, except those of the control group (G1) were exposed to CS daily for 10 min to induce chronic bronchitis. After 15 days of CS-exposure animals of groups 3, 4 were treated with Bresol at a dosage of 250 and 500 mg/kg body weight/day PO, respectively, 2 h post CS-exposure. This treatment schedule along with CS-exposure was continued for 5 weeks. Animals in group 2 were maintained as untreated positive control and received only vehicle. At the end of the treatment period, bronchoalveolar lavage fluid (BALF) was collected; total protein and TNF-α was estimated in BALF.

The daily exposure of animals to CS showed significant elevation of proinflammatory cytokine, TNF-α, and total protein content in BALF indicating the ongoing inflammatory process in the airway tissues. The histopathological findings further confirmed the presence of pathological lesions in the lungs of CS-exposed rats. Treatment with Bresol showed significant dose-dependent anti-inflammatory effect against CS-induced airway inflammation as indicated by reduced levels of TNF-α and total protein in BALF.
Another study documented a decrease in histamine release from mast cells (humoral immune responses) and in leukocyte migration inhibition (cell-mediated immune responses). This immunomodulatory effect was postulated as mediated by gamma aminobutyric acidergic pathways. Kelm et al documented an antioxidant bioassay of *O sanctum* (which yielded cirsilineol, cirsimaritin, isothymusin, isothymolin, apigenin, rosmarinic acid, and eugenol) and in addition observed a potent anti-inflammatory (COX-1 and COX-2 inhibitory) activity. According to a study, *O sanctum* was found to possess significant anti-inflammatory activity against PG-E2, leukotriene, and arachidonic acid, and the results of the same study suggested that *O sanctum* has the capacity to block both the COX and LO pathways of arachidonate metabolism. Singh et al observed significant inhibition of leucocyte migration in the pleural exudates; this suggests that *O sanctum* inhibits the enhancement of vascular permeability and leucocyte migration after inflammatory stimulus. Analgesic action of *O sanctum* is exerted both centrally as well as peripherally. Balanerhu et al observed the free radical scavenging potential of ursolic acid isolated from *O sanctum* against lipid peroxidation in vitro. Orientin and vicenin (isolated from *A vasica*) demonstrated the potent free radical scavenging activity of *A vasica* to be similar to that of codeine, in vitro. The principle ingredients of *C rotundus* consist of 4 sesquiterpenes (beta-selinene, isocurcumenol, nootkatone, and aristolone) and a triterpene (oleanolic acid). Seo et al observed the inhibition of NO and O2- productions in vitro by *C rotundus*. This inhibition was due to the suppression of iNOS protein as well as iNOS messenger RNA expression. *T belerica* has a potent antifungal activity. Embelin, a benzoquinone-derivative isolated from *E ribs*, when tested for its antibacterial potential exhibits a significant inhibition against 5 strains and moderate activity against 3 strains of the 12 bacteria tested. Embelin and its 2,5-isobutylmine salts have been reported to possess anti-inflammatory activity in carragenan-induced paw edema and cotton pellet granuloma formation.

The aqueous fruit extract of *Terminalia chebula* has been investigated for its effect on cell-mediated and humoral components of the immune system in mice. Administration of *T chebula* extract in mice produced an increase in humoral antibody titer and delayed-type hypersensitivity. It was concluded that *T chebula* extract is a promising drug with immunostimulant properties. Aqueous extract of *T chebula* was tested for potential antioxidant activity by examining its ability to inhibit γ-radiation-induced lipid peroxidation in rat liver microsomes and to damage superoxide dismutase enzyme in rat liver mitochondria. The antimitogenic activity of the extract has been examined by following the inhibition of γ-radiation-induced strand breaks formation in plasmid pBR322 DNA, which showed the presence of compounds such as ascorbate, gallic acid, and ellagic acid. The extract inhibits xanthine/xanthine oxidase activity and is also an excellent scavenger of 1,1-diphenyl-2-picyrylhydrazyl (DPPH) radicals. In addition, the extract showed antimicrobial activity against 2 dental caries causing bacteria (*Streptococcus mutans* and *Staphylococcus aureus*). Highest mean diameter of inhibition zone was produced by the acetone extracts of 25.32 mm and a minimum inhibitory concentration (MIC) of 25 mg/mL against *S mutans* and by the acetone extracts of 32.97 mm and a MIC of 12.5 mg/mL against *S aureus*.

In the present study, the effect of isolated piperine from *Piper nigrum* fruits on memory and behavior mediated through monoamine neurotransmitters was investigated. Piperine isolated from *P nigrum* exhibited prominent nootropic activity, reversed clonidine-induced hypothermia, decreased lithium-induced head twitches, and significantly delayed haloperidol-induced catalepsy at a dose of 10 mg/kg. It also modified 5-hydroxytryptamine and noradrenaline-mediated behavior. Therefore, piperine can be used as a potential nootropic agent. The various biological determinants such as oxidative stress markers (reactive oxygen species and glutathione), Bcl-2 protein expression, mitochondrial membrane potential, caspase-3 activity, DNA damage, splenic B and T-cell population, blastogenesis, and cytokines (IL-2 and γ-IFN)
were measured to ascertain its cell protective potential. The reported free radical scavenging property of piperine and its antioxidant potential could be responsible for the modulation of intracellular oxidative stress signals. These in turn appear to mitigate the apoptotic pathway and other cellular responses altered by cadmium.

The bark of *C. zeylanicum* showed a very low inhibitory concentration value ranging from 0.14 to 0.26 mg/mL, efficiency concentration value from 6.1 to 11.6 mg/mg DPPH, and reducing power value from 0.6 to 2.8 ascorbic acid equivalents (ASE/mL), and reasonably high values (8.5–16.2) of anti-radical power, indicating their strong free radical scavenging activity. It also showed better inhibition of hydroxyl radical induced deoxyribose degradation.

The high dose of cinnamon bark (100 mg/kg per os) decreased *Pasteurella multocida*-induced mortality by 17% and increased the phagocytic index in carbon clearance test, neutrophil adhesion, serum immunoglobulin levels, and antibody titer values. The anti-inflammatory effect of this plant was determined by xylene-induced ear edema in mice and cotton plant was determined by xylene-induced edema, cotton pellet granuloma, and granuloma pouch techniques in normal and adrenalectomized rats. The antibacterial efficacy of the methanol extract of *M. ferrea* flowers could inhibit a large number of Gram-positive and Gram-negative bacteria at concentration ranges of 50 to 100 µg/mL, or even lower, as against vibrios and *Escherichia coli*. In in-vivo tests, used at concentrations of 100 and 200 µg/g of body weight, it offered significant protection to Swiss strain of albino mice when challenged with 50 median lethal doses (MLD) of a virulent strain (*Salmonella typhimurium*).

**References**


**Conclusion**

Increasing prevalence of upper and lower respiratory tract allergic diseases in children is an area of concern due to associated long-term compromises in the quality of life. The available treatment options for these diseases have major limitations owing to low efficacy, associated adverse events, and compliance issues. This study observed an excellent and rapid symptomatic control in allergic rhinitis, allergic bronchitis, and asthmatic bronchitis (with improvement in PEFR).

Therefore, it can be concluded that Bresol (HK-07) tablets are clinically effective and safe in children suffering from allergic rhinitis, allergic bronchitis, or asthmatic bronchitis.
Sengupta K, et al. Bresol Tablets in Respiratory Tract Allergic Diseases

Evaluation of Efficacy and Safety of Bresol (HK-07) Syrup in Pediatric Allergic Rhinitis

Chatterjee S, et al


ABSTRACT

This study was conducted to evaluate the clinical efficacy and safety (short- and long-term) of Bresol (HK-07) syrup in children suffering from AR. The study was an open, non-comparative, phase III clinical trial, which included 110 children between the age group of 3 to 12 years who presented with symptoms of AR (sneezing, nasal congestion, itching of the eyes and nose, postnasal drip, rhinorrhea, and watery eyes). At initial visit, a detailed medical history was obtained by interviewing the child and parent, followed by thorough clinical examination, with special emphasis on upper respiratory system examination. Each child was advised to consume one teaspoon of Bresol (HK-07) syrup twice daily for 4 weeks. All children were followed up on a weekly basis for a period of 1 month. At each follow-up visit, clinical examination was done for evaluating symptomatic improvement of rhinitis.

Out of 110 enrolled children, 25 (22.72%) children were lost to follow-up and the remaining 85 (77.27%) children's data analyzed. There was a highly significant reduction in mean scores for symptomatic evaluation of sneezing, nasal congestion, itching of the eyes and nose, postnasal drip, rhinorrhea and watery eyes at the end of 1 week and almost all children were symptom-free at the end of 1 month. The pathological changes in levels of hematological and biochemical parameters noted at the time of the enrollment were renormalized at the end of the study, without any clinically significant adverse events. Therefore, it can be concluded that Bresol (HK-07) syrup is clinically effective and safe in children suffering from AR.

Introduction

Allergic rhinitis (AR) is one of the most common pediatric chronic diseases. However, its exact prevalence is very difficult to ascertain. Almost half of new patients examined by a pediatrician have symptoms and signs related to upper respiratory allergies. The prevalence of AR increases with age (approximately 1% infants, 5% children aged 5 to 9 years, and 15% adolescents have AR). Infants ≤ 6 months old are rarely sensitized to aeroallergens (crawling exposes infants to allergens) and by 2 years of age approximately 20% of children with chronic respiratory symptoms have positive skin test results, especially to indoor aeroallergens. AR often coexists with infectious rhinitis. Clinically, AR presents with acute nasal congestion, increased mucus production, airflow obstruction, mucosal edema, obstruction of mucosal drainage, and sinus ostia (mucosal edema and obstruction of sinus ostia predispose the affected child to sinusitis and asthma). AR impacts the quality of life of children and their families. Sleep
disturbances and daytime fatigue related to AR lead to decreased attention, impaired learning, and poor school performance. AR also affects social development. Associated conditions such as otitis media with effusion may impact hearing and speech development.

Patients with AR typically require multiple medications as no single drug relieves all symptoms of AR. Currently available treatment options for AR have major limitations due to low efficacy, associated adverse events, and compliance issues. Antihistamines, sympathomimetics and xanthine derivatives are commonly used as the first-line treatment for symptomatic management, but they do not prevent recurrent episodes. Antihistamines reduce sneezing, itching, and rhinorrhea, but not congestion and obstruction. Use of glucocorticosteroids and anticholinergics is questionable due to long-term adverse effects. Prophylactic use of mast cell stabilizers has the disadvantage of frequent administration. Decongestant drugs are effective in the treatment of nasal obstruction, but do not improve other symptoms of rhinitis and have high incidence of adverse effects. Studies with leukotriene receptor antagonists as a sole therapy in these allergic diseases have proved disappointing.

Bresol (HK-07) syrup is a polyherbal formulation indicated in the management of AR. Bresol (HK-07) syrup contains extracts of *Curcuma longa*, *Ocimum sanctum*, *Adhatoda vasica*, *Trikatu*, *Triphala*, *Embelia ribes*, *Cyperus rotundus*, *Cinnamomum zeylanicum*, *Elettaria cardamomum*, *Cinnamomum tamala*, and *Mesua ferrea*. This study was planned to evaluate the efficacy and safety of Bresol (HK-07) syrup in AR.

### Table 1. Reduction in Mean Scores for Sneezing, Nasal Congestion, Itching of Eyes, Itching of Nose, Postnasal Drip

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
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<tr>
<td>Sneezing</td>
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<td>5.564</td>
<td>3.736</td>
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<td></td>
<td>SD</td>
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<td>2.248</td>
<td>2.718</td>
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<td></td>
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<td>0.09443</td>
<td>0.2144</td>
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<td>F</td>
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<td>200.2</td>
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<tr>
<td>R²</td>
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<td>0.6475</td>
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</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;.0001</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| Nasal congestion      | Mean     | 7.900  | 5.555  | 3.709  | 3.027  | 3.036  |
|                       | SD       | 0.9082 | 2.030  | 2.607  | 2.891  | 2.911  |
|                       | SEM      | 0.08659| 0.1936 | 0.2485 | 0.2756 | 0.2776 |
| F                     |          | 217.4  |        |        |        |        |
| R²                    |          | 0.6660 |        |        |        |        |
| P                     |          | <.0001 |        |        |        |        |

| Itching of the eyes   | Mean     | 6.883  | 4.541  | 3.000  | 2.387  | 2.450  |
|                       | SD       | 1.571  | 2.335  | 2.646  | 2.790  | 2.844  |
|                       | SEM      | 0.1491 | 0.2216 | 0.2511 | 0.2648 | 0.2699 |
| F                     |          | 159.3  |        |        |        |        |
| R²                    |          | 0.5916 |        |        |        |        |
| P                     |          | <.0001 |        |        |        |        |

| Itching of the nose   | Mean     | 7.064  | 4.618  | 2.982  | 2.327  | 2.382  |
|                       | SD       | 1.350  | 2.246  | 2.640  | 2.793  | 2.835  |
|                       | SEM      | 0.1287 | 0.2142 | 0.2518 | 0.2663 | 0.2703 |
| F                     |          | 172.6  |        |        |        |        |
| R²                    |          | 0.6129 |        |        |        |        |
| P                     |          | <.0001 |        |        |        |        |

| Watery eyes           | Mean     | 5.963  | 4.130  | 2.639  | 2.194  | 2.194  |
|                       | SD       | 1.981  | 2.431  | 2.515  | 2.537  | 2.537  |
|                       | SEM      | 0.1906 | 0.2339 | 0.2420 | 0.2442 | 0.2442 |
| F                     |          | 157.4  |        |        |        |        |
| R²                    |          | 0.5952 |        |        |        |        |
| P                     |          | <.0001 |        |        |        |        |

| Rhinorrhea            | Mean     | 7.800  | 5.300  | 3.355  | 2.764  | 2.773  |
|                       | SD       | 1.047  | 2.212  | 2.830  | 2.943  | 2.957  |
|                       | SEM      | 0.09987| 0.2109 | 0.2699 | 0.2806 | 0.2820 |
| F                     |          | 234.3  |        |        |        |        |
| R²                    |          | 0.6825 |        |        |        |        |
| P                     |          | <.0001 |        |        |        |        |

| Postnasal drip        | Mean     | 5.636  | 4.182  | 2.682  | 2.327  | 2.327  |
|                       | SD       | 2.196  | 2.546  | 2.556  | 2.693  | 2.693  |
|                       | SEM      | 0.2093 | 0.2427 | 0.2437 | 0.2567 | 0.2567 |
| F                     |          | 172.6  |        |        |        |        |
| R²                    |          | 0.6129 |        |        |        |        |
| P                     |          | <.0001 |        |        |        |        |

SD, standard deviations; SEM, standard error of the mean
Repeated measures analysis of variance (ANOVA) with Bonferroni’s multiple comparison test statistics were used.

**Aim**

This study was planned to evaluate the clinical efficacy, short-term and long-term safety of Bresol (HK-07) syrup in children (in the age group of 2–12 years) suffering from AR.

**Study Design**

The study was an open, noncomparative, phase 3 clinical trial conducted at the Department of Pediatrics, Medical College, Kolkata, from April 2003 to March 2004, as per the ethical guidelines of the Declaration of Helsinki. The study protocol, case report forms (CRF), regulatory clearance documents, product related information, and informed consent form (ICF), in English and Bengali, were submitted to the Institutional Ethics Committee and approved.
Materials and Methods

Inclusion criteria
One hundred and ten children in the age group of 3 to 12 years who presented with symptoms of AR (sneezing, nasal congestion, itching of the eyes and nose, postnasal drip, rhinorrhea, and watery eyes) were included in the study.

Exclusion criteria
Severely malnourished children and children with severe systemic illness were excluded from the study.

Study procedures
The children and/or their parents/guardians were informed about the study drug, its effects, duration of the study, their responsibilities, importance of compliance, patient’s rights, ethical aspects, and overall plan of the study. Informed consent was obtained from parents/guardians of all included children and a witness unrelated to the clinical trial attested the same.

At initial visit, a detailed medical history was obtained by interviewing the child and parent/guardian, which was followed by thorough clinical examination, with special emphasis on upper respiratory system examination. The details of the clinical examination were recorded in the CRF. All children underwent hematological and biochemical tests (Hb, TLC, DLC, ESR, WBC, ESR, RBC, TLC). Each child was advised to consume one teaspoon of Bresol (HK-07) syrup twice daily for 1 month.

Examinations
At each follow-up visit, clinical examination was done for evaluating symptomatic improvement of rhinitis (sneezing, nasal congestion, itching of the eyes and nose, postnasal drip, rhinorrhea, and watery eyes). All children were investigated by hematological and biochemical tests (Hb, TLC, DLC, ESR, WBC, RBC), at the end of 1 month.

Adverse events
All adverse events either reported or observed by patients were recorded in CRF with information about severity, onset, duration, and action taken regarding the study drug. Relation of adverse events to study medication was predefined as “unrelated,” a reaction that does not follow a reasonable temporal sequence from the time of administration of the drug; “possible,” follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient; and “probable,” follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state.

Primary and secondary end points
The predefined primary endpoints were rapid symptomatic control, clinical, biochemical, and hematological improvements. The predefined secondary endpoints were incidences of short-term and long-term adverse events and overall compliance to the drug treatment.

Statistical analysis
Statistical analysis was carried out according to intention-to-treat principles. Changes in various
Table 2. Decreased Levels of TLC, AEC, ESR, Monocytes, Eosinophils, Lymphocytes, and Neutrophils

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (cells/cu.mm)</td>
<td>13,246</td>
<td>10,751</td>
<td>7.704</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>SD</td>
<td>4000</td>
<td>2493</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>388.5</td>
<td>265.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEC (cells/cu.mm)</td>
<td>702.6</td>
<td>319.9</td>
<td>8.630</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>SD</td>
<td>527.3</td>
<td>353.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>51.21</td>
<td>38.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>13.65</td>
<td>10.16</td>
<td>8.893</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>SD</td>
<td>5.457</td>
<td>3.248</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.5351</td>
<td>0.3462</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>1.937</td>
<td>0.8734</td>
<td>6.465</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>SD</td>
<td>1.453</td>
<td>0.8529</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.1635</td>
<td>0.09595</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>5.777</td>
<td>3.667</td>
<td>3.409</td>
<td>.0012</td>
</tr>
<tr>
<td>SD</td>
<td>4.640</td>
<td>5.900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.4572</td>
<td>0.7433</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>38.65</td>
<td>35.15</td>
<td>5.677</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>SD</td>
<td>9.121</td>
<td>8.985</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.9668</td>
<td>0.8768</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>58.66</td>
<td>58.47</td>
<td>2.026</td>
<td>.0459</td>
</tr>
<tr>
<td>SD</td>
<td>8.269</td>
<td>7.482</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0.8032</td>
<td>0.8021</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AEC, absolute eosinophils count; ESR, erythrocyte sedimentation rate; TLC, total lymphocyte count; SD, standard deviation; SEM, standard error of the mean; Statistical analysis was carried out using paired t-test.

Results

Out of 110 enrolled children, 25 (22.72%) children were lost to follow-up and the remaining 85 (77.27%) children’s data were analyzed. There was a highly significant reduction in mean scores of symptoms, such as sneezing, nasal congestion, itching of the eyes and nose, postnasal drip, rhinorrhea, and watery eyes at the end of 1 week and almost all children were symptom-free at the end of 1 month (Table 1). The increased levels of TLC (Figure 1), eosinophils (Figure 2), AEC (Figure 3), lymphocytes (Figure 4), polymorphs and ESR (Figure 5) noted at the time of the enrollment decreased significantly at the end of the study (Table 2). There were no clinically significant adverse events either reported or observed, during the entire study period.

Discussion

The pathophysiology of AR is complex and is influenced by a number of factors. Genetic factors determine total IgE levels, the child’s response to the environment influences the development of AR. It has been observed that 60% of children with AR have a family history of allergy. Activation of the atopic response requires 2 distinct phases of immune system activity. Initial exposure to the antigen leads to sensitization of the immune system and subsequent exposures result in the atopic reaction. Aeroallergens are inhaled and deposited on the mucosal surfaces of the upper respiratory tract and are processed by macrophages that activate B cells to produce IgE. Helper T cells influence the immune system response to an antigen and Th-1 cells direct cell-mediated responses, while Th-2 cells orchestrate the atopic response. In atopic patients, helper T cells may preferentially differentiate into Th-2 cells that release IL-3, IL-4, IL-5, IL-8, IL-10, and IL-13. Wahn et al demonstrated that allergic sensitization in children is related to exposure levels of indoor allergens. Kulig et al suggested that the predisposition to allergic conditions and at least 2 seasons of pollen exposure...
allergen exposure are necessary before AR is clinically manifested. Antigen specific IgE molecules are bound by mediator cells (eosinophils, basophils, and mast cells) in preparation for the reaction phase. Additional antigen exposure initiates the early phase of atopic response (a Gell and Coombs type I hypersensitivity reaction). Within minutes, due to cellular signaling, there is a release of mediators for eosinophils, mast cells, and basophils (including histamines, neutral proteases, acid hydrolases, cathepsin G, and carboxypeptidases). Histamines influence vasodilation in the mucosa, kinins cause edema and congestion, prostaglandins (PGs) promote nasal itching and leukotrienes (LT) cause sneezing and stimulate watery secretions.

The late-phase response is influenced by factors released primarily by mast cells and basophils (lipid mediators [LTs] and PGs) and cytokines [IL and TNF, tumor necrosis factor-α]). The increased vascular permeability, continued tissue edema, and cellular recruitment following antigen exposure lead to the obstructive symptoms. Continued inflammation causes loss of surface epithelium and thickening of basement membrane. Hyperplasia of mucus-producing cells increases secretions and alters mucus composition. Ciliary dyskinesia further impairs mucus transport and nasal airflow. Nasal hyperreactivity is also related to increased levels of nerve growth factor (NGF) in the nasal mucosa and increased secretions in patients with perennial AR, which may lead to changes in sensory nerve sensitivity in the mucosa. In patients who remain in a continuous late-phase response, inflammatory cells release more mediators and increase hyperactivity to histamines and nonallergic stimuli (tobacco smoke). The accumulation of inflammatory cells and mucosal injury causes priming of the nasal mucosa, as smaller amounts of allergen are required to elicit further response.

Children with AR, due to sensitivities to perennial allergens are less likely to have their condition resolved than children with other types of AR. Children commonly develop sensitivity to dust, mites, cockroaches, pets, indoor molds, and food. Food allergies may have cutaneous, gastrointestinal, and nasal manifestations. In infancy, food allergies are more common than inhalant allergies and non-breast-fed infants are more likely to develop food sensitivities at an early age, especially to milk. AR appears to precede the development of asthma and atopys is “the strongest identifiable predisposing factor for the development of asthma.” Although treatment for AR may not prevent the development or improve asthma, appropriate management is likely to prevent its exacerbation.

Itching and sneezing are the most common symptoms of AR and the associated symptoms include rhinorrhea, postnasal drip, palatal and ocular pruritis, excessive lacrimation, and nasal obstruction. Treatment is directed toward reducing inflammation and alleviating symptoms and includes a combination of environmental precautions, pharmacotherapy, and immunotherapy.

This study observed an excellent and rapid symptomatic control, which was evident by significant reduction in the mean scores for sneezing, nasal congestion, itching of the eyes and nose, postnasal drip, rhinorrhea, and watery eyes at the end of study. The pathological changes in the levels of hematological and biochemical parameters noted at the time of the

Pharmacodynamic Study of Bresol Syrup

In this study, the effect of Bresol on active anaphylaxis in inbred Wistar rats (175–200 g), housed in standard conditions, was studied.

Twenty-eight rats were sensitized by injecting 0.5 mL of horse serum, subcutaneously, along with 0.5 mL of triple antigen (comprising 20,000 million *Bordetella pertussis*). The sensitized rats were divided into 4 groups of 7 animals each. Group I served as control, while groups II, III, and IV were orally administered with Bresol at a dose of 0.78125, 1.5625, and 3.125 mL/kg body weight, once a day, for 14 days. On day 14, after 2 h of treatment, the rats were challenged with intravenous injection of 0.25 mL horse serum and then observed for the onset, and duration of persistence of symptoms (such as dyspnea and cyanosis). Results showed that, in control rats, intravenous challenge dose of the antigen (horse serum) caused shock in 100% of the animals, while in rats treated with 3.125 mL/kg body weight delayed the onset of symptoms of shock (*P* < .001) and reduced severity of symptoms (*P* < .05) as well as the mortality rate (*P* < .05). Bresol at a dose of 3.125 mL/kg body weight also resulted in significant reduction of serum IgE levels (25.80 ± 4.85 ng/mL, *P* < .001) as compared to sensitized controls (125.06 ± 9.66 ng/mL). Serum IgE levels in the control group was 8.83 ± 0.84 ng/mL (*P* < .001 as compared to sensitized control). Bresol showed optimal pharmacological effect at the dose of 1.5625 mL/kg body weight.

These findings lend credence to the beneficial use of Bresol syrup in the treatment of asthma and related conditions.
enrollment were also renormalized without any clinically significant adverse events. This excellent outcome might be due to the synergistic actions of the ingredients of Bresol (HK-07) syrup.

In various animal and human studies, curcuminoids-I, II and III (components of *C. longa*) have been shown to inhibit a number of molecules involved in inflammation (phospholipase, LO, cyclooxygenase-1 [COX-1] and -2, LT, TX, PGs, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemo-attractant protein-1, IFN-inducible protein, Tumor necrosis factor [TNF], and IL-12). Curcumin has been reported to have anti-allergic property, as tested in an in vitro model of airway hyperresponsiveness. Inhibition of LO was shown to be due to the ability of curcumin to bind with phosphatidylcholine micelles. Enhanced suppression of COX-2 expression was observed due to extracellular signal-related kinase activity and nuclear factor κB [NF-κB] activation inhibition, which might be the molecular mechanisms of actions of curcumin. Kang et al., observed that curcumin significantly inhibited production of IL-12, reduced induction of IFN-γ, IL-4 in CD4+ T-cells by macrophages, leading to the inhibition of Th-1 cytokine profile ([IFN-γ and IL-4 production] in CD4+ T-cells. Curcumin is a potent antioxidant and it inhibits Ca2+ entry and protein kinase C activity. Curcumin also has an immunostimulatory activity and hence increases the circulating antibody titer, plaque forming cells, alpha-esterase positive cells, and phagocytosis. Gingerols and diarylhepatanoids are the active ingredients of *Zingiber officinale*, which are potent inhibitors of prostaglandin biosynthesizing enzyme (PG synthetase). The structure of these compounds indicates that these inhibitors might also be active against arachidonate 5-LO (an enzyme of leukotriene biosynthesis). Umeda et al., recorded that *Z. officinale* inhibited biotransformation of AA comparable to indomethacin. The other ingredients of *Z. officinale*, namely oleoresins ([8]-paradol, [8]-shogaol) have inhibitory effects on COX-2 enzymes and the mechanism of action was hypothesized by the attenuation of COX-1/TX synthase enzymatic activity. COX-1 and COX-2 (regulated by the eukaryotic transcription factor NF-κB) have been recognized as molecular targets for actions of *Z. officinale*, and [6]-gingerol acts by interfering with intracellular signaling cascades, those involving NF-κB and mitogen-activated protein kinases. Thomson et al., documented significant inhibitory effects of *Z. officinale* on PG-E2 production. Ahmed et al. observed that the antioxidant effect of *Z. officinale* was comparable to ascorbic acid as demonstrated by lowered lipid peroxidation, while maintaining the activities of other antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase). [6]-Gingerol was found to be a potent inhibitor of inducible nitric oxide synthase and also an effective protector against peroxynitrite-mediated damage. Wilasrusmee et al., reported the immunosuppressive effects of *Z. officinale* in vitro as evident by the decreased responsiveness in lymphocyte culture. The *Z. officinale* extract had been shown to raise the thymus index, spleen index, phagocytosis, and rate of α-naphthyl acetate esterase and titer of IgM, which indicates immunostimulation. Dihydrokawain, yangonin, and methysticin are the principle anti-inflammatory ingredients of *Piper longum*. Choudhary et al. documented that *P. longum* inhibits the lipid peroxidation process effectively by its ability to scavenge free radicals involved in initiation and propagation steps. Chiu et al. observed that *P. longum* retards the macrophage recruitment and suppresses cytokine production. Hashimoto et al. isolated kava pyrones from *P. longum* and recorded inhibition of TNF-α release.

Tannoids (emblicanin A and B, punigluconin, and pedunculagin) are the principle ingredients of *Emblica officinalis*. In addition to the antitussive activity, it was observed that *E. officinalis* has anti-inflammatory, antispasmodic, and antioxidant efficacies and it reduces the mucus secretion in the airways. Khanom et al. identified the strong superoxide-scavenging and prolyl endopeptidase inhibitory activity of *E. officinalis*. Sai Ram et al. observed that *E. officinalis* significantly inhibited free radical production, restored the antioxidant status, inhibited apoptosis and DNA fragmentation, relieved the immunosuppressive effects on lymphocyte proliferation and even restored the IL-2 and γ-IFN production. In another study, it was observed that *E. officinalis* acts as an immunomodulator and decreases the induction of iNOS. One study reported that, *E. officinalis* enhanced cell survival, decreased free radical production and ensured higher antioxidant levels, inhibited induced immunosuppression and restored both phagocytosis and γ-IFN production by macrophages.

Tasaduq et al. demonstrated potent anti-oxidative activity of *Terminalia belerica*. *T. belerica* inhibited lipid peroxide formation by scavenging hydroxyl and superoxide radicals in vitro.
observed the antioxidant potential of *T. bellerica* (stronger than alpha-tocopherol), which was attributed to hydroxybenzoic acid and hydroxycinnamic acid derivatives, flavonol glycosides, and their isoflavones.58

Godhwani *et al.* documented that *O. sanctum* has an immunostimulatory effect on the humoral immunologic response (an increase in antibody titer), as well as on the cellular immunologic response (E-rosette formation and lymphocytosis).59 Another study documented a decrease in histamine release from mast cells (humoral immune responses) and a decrease in leucocyte migration inhibition (cell-mediated immune responses). This immunomodulatory effect was postulated as mediated by γ-aminobutyric acidergic pathways.60 Kelm *et al.* documented an antioxidant bioassay of *O. sanctum* (which yielded cirsilolinol, cirsimaritin, isothymusin, isothymonin, apigenin, rosmarinic acid, and eugenol) and in addition observed a potent anti-inflammatory (COX-1 and COX-2 inhibitory) activity.61 *O. sanctum* was found to possess significant anti-inflammatory activity against PG-E2, leukotriene and AA, and the results suggested that *O. sanctum* has the capacity to block both the COX and LO pathways of arachidonate metabolism.62 Singh *et al.* observed significant inhibition of leucocyte migration in the pleural exudates, which suggest that the *O. sanctum* inhibits enhancement of vascular permeability and leucocyte migration following inflammatory stimulus.63 Analgesic action of *O. sanctum* is exerted both centrally as well as peripherally.64 Balanehru *et al.* observed the free radical scavenging potential of ursolic acid isolated from *O. sanctum* against lipid peroxidation in vitro.65 Maulik *et al.* demonstrated the potent free radical scavenging activity.66 Orientin and vicenin (isolated from *O. sanctum*) have strong antioxidant activity.67

The widely used mucolytics, namely benzylamines (bromhexine and ambroxol) are the semi-synthetic derivatives of vasicine extracted from *A. vasica*, and these benzylamines enhance lysozyme levels in respiratory tract secretions and clear bacilli-laden mucus.68 Chakraborty *et al.* reported the potent anti-inflammatory activity of *A. vasica* to be equivalent to that of hydrocortisone.69 Paliwa *et al.* documented the potent anti-allergic activity of “Compound 73/602 (AA)” (a structural analog of vasicinone, an alkaloid of *A. vasica*).70 Dhuley *et al.* reported the antitussive activity of *A. vasica* to be similar to that of codeine in vitro.71

The principle ingredients of *C. rotundus* are 4 sesquerpenes (beta-selinene, isocurcumol, nootkatone, and aristolone) and a triterpene (oleanolic acid).72 Seo *et al.* observed inhibition of NO and O₂-production in-vitro by *C. rotundus* and the inhibition was due to the suppression of iNOS protein, as well as iNOS messenger RNA expression.73

*T. bellerica* has a potent antifungal activity.74

Embelin, a benzoquinone-derivative isolated from *E. ribes*, when tested for its antibacterial potential exhibits significant inhibition against 5 strains and moderate activity against 3 strains of the 12 bacteria tested.75 Embelin and its 2,5-isobutylinine salts have been reported to possess anti-inflammatory activity in carrageenan-induced paw edema and cotton pellet granuloma formation.76

The aqueous fruit extract of *T. chebula* has been investigated for its effect on cell-mediated and humoral components of the immune system in mice. Administration of *T. chebula* extract produced an increase in humoral antibody titer and delayed-type hypersensitivity in mice. It was concluded that the *T. chebula* extract is a promising drug with immunostimulant properties.77 Aqueous extract of *T. chebula* was tested for potential antioxidant activity by examining its ability to inhibit γ-radiation-induced lipid peroxidation in rat liver microsomes and damage to superoxide dismutase enzyme in rat liver mitochondria. The antimutagenic activity of the extract has been examined by following the inhibition of γ-radiation-induced strand breaks formation in plasmid pBR322 DNA, which showed the presence of compounds such as ascorbate, gallic acid, and ellagic acid. The extract inhibits xanthine/xanthine oxidase activity and is also an excellent scavenger of DPPH radicals.78 The extracts show antimicrobial activity against 2 dental caries causing bacteria, that is, *Streptococcus mutans* and *Staphylococcus aureus*. Highest
mediated through monoamine neurotransmitters was investigated. Piperine isolated from *P. nigrum* exhibited prominent nootropic activity, reversed clonidine-induced hypothermia, decreased lithium induced head twitches and significantly delayed haloperidol-induced catalepsy at a dose of 10 mg/kg. The alkaloid modified 5-HT and NA-mediated behavior. Hence, piperine from the fruits of *P. nigrum* can be used as a potential nootropic agent. The various biological determinants such as oxidative stress markers (reactive oxygen species and GSH), Bcl-2 protein expression, mitochondrial membrane potential, caspase-3 activity, DNA damage, splenic B- and T-cell population, blastogenesis and cytokines (IL-2 and γ-IFN) were measured to ascertain its cell protective potential. The reported free radical scavenging property of piperine and its antioxidant potential could be responsible for the modulation of intracellular oxidative stress signals. These in turn appear to mitigate the apoptotic pathway and other cellular responses altered by cadmium.

The bark of *C. zeylanicum*, showed a very low inhibitory concentration value ranging from 0.14 to 0.26 mg/mL, efficiency concentration value from 6.1 to 11.6 mg/mg DPPH and reducing power value from 0.6 to 2.8 ascorbic acid equivalents (ASE/mL), and reasonably high values (8.5–16.2) of anti-radical power (ARP), indicating their strong free radical scavenging activity. They also showed better inhibition of hydroxyl radical-induced deoxyribose degradation. The high dose of cinnamon bark (100 mg/kg po) decreased *Pasteurella multocida*-induced mortality by 17%, increased the phagocytic index in carbon clearance test, increased neutrophil adhesion, increased serum immunoglobulin levels and antibody titer values. The anti-inflammatory effect of these plants was determined by xylene-induced ear edema in mice and cotton pellet granuloma test in rats. The anti-nociceptive effect of ethanolic extract of *C. zeylanicum* is studied using the acetic acid-induced writhing and hot plate test in mice. It showed an antinociceptive effect against both acetic acid-induced writhing and hot plate-induced thermal stimulation.

Leaves of *C. tamala* significantly and dose-dependently inhibited edema induced by carrageenan in rats and also significantly reduced acetic acid-induced vascular permeability in mice. When tested in vitro, it exhibited significant membrane stabilizing property.

*E. cardamomum* significantly increased WBC count. Similarly, bone marrow cellularity and alpha esterase positive cells, which are lowered by radiation, were partly restored by *E. cardamomum*. It induced morphological perturbation in mice’s heart. The results show an inhibitory effect of glyceraldehyde 3-phosphate dehydrogenase and an impotent increase in the level of thiobarbituric acid reactive substances, succinate dehydrogenase, and catalase activities.

The xanthones of *M. ferrea* namely, dehydrocycloguanandin, calophyllin-B, jacareubin, 6-desoxy jacareubin, mesuxanthone-A, mesuxanthone-B, and euxanthone produced varying degrees of CNS depression and also exhibited anti-inflammatory activity both by intraperitoneal and oral routes in rats as tested by carrageenin-induced hind paw edema, cotton pellet granuloma and granuloma pouch techniques, in normal and adrenalectomized rats. The antibacterial efficacy of the methanol extract of flowers of *M. ferrea* could inhibit a large number of Gram-positive and Gram-negative bacteria at concentration ranges of 100 to 50 µg/mL, or even lower, as against vibrios and *Escherichia coli*. In in vivo tests, used at concentrations of 100 and 200 µg/g of body weight, it offered significant protection to the Swiss strain of albino mice when challenged with 50 MLD of a virulent strain *Salmonella typhimurium*.

**Conclusion**

Increasing prevalence of AR in children is a global issue of concern, due to associated long-term compromises in the quality of life. The available treatment options for these diseases have major limitations due to low efficacy, associated adverse events and compliance issues. This study observed an excellent, rapid symptomatic control in AR. The pathological changes in levels of hematological and biochemical parameters noted at the time of the enrollment were renormalized at the end of the study, without any clinically significant adverse events. Therefore, it can be concluded that Bresol (HK-07) syrup is clinically effective and safe in children suffering from AR.

**References**


Clinical Practice Pearls

Petroleum Ether Extract of *Cissus quadrangularis* Enhances Bone Marrow Mesenchymal Stem Cell Proliferation and Facilitates Osteoblastogenesis

Potu BK. *Clinics (Sao Paulo)*. 2009;64(10): 993–998.

Introduction

The repair of bone defects, secondary to trauma, osteoporosis, osteomyelitis, and nonunion fracture poses a significant problem for many clinicians, particularly orthopedic, head and neck, and plastic surgeons. Several strategies have been used to promote the bone-healing process. Bone marrow mesenchymal stem cells (MSCs) have recently received widespread attention due to their potential use in tissue engineering applications. MSCs are defined as self-renewable, multipotent progenitor cells with the capacity to differentiate into several distinct mesenchymal lineages and are thus excellent candidates for tissue engineering.

As a part of a continuing search for biologically active natural anti-osteoporotic agents, this study has extensively evaluated the efficacy of petroleum ether extract of *Cissus quadrangularis* Linn. (CQ) on osteomodulation in a rat model. CQ (Veldt Grape or Winged Trebeine), a vine that belongs to the family Vitaceae, is one of the most commonly used medicinal plants in India. This is an edible plant found in the warmer regions of India, Sri Lanka, Malaysia, Java, and West Africa. The plant, commonly known as “bone setter,” is referred to as Asthisandhani in Sanskrit and Hadjod in Hindi because of its ability to join bones. The plant and its medicinal properties have been described in ancient books such as Bhava Prakash. The fresh stem and leaves of CQ are used for the treatment of hemorrhoids, menstrual disorders, scurvy, and flatulence. Extracts of this plant are reported to contain phytoestrogenic steroids, ascorbic acid, carotene, calcium, and anabolic steroids. The plant extract has been shown to have bone fracture-healing properties in several in-vivo studies. Another study reported the antibacterial and antioxidant activities of the CQ extract. Various formulations now contain extracts of CQ in combination with other compounds to manage overweight conditions and obesity as well as to treat complications resulting from these conditions, notably metabolic syndrome (syndrome X). CQ was also recently shown to have significant effects on periodontal regenerative therapy. Using an ovariectomized rat model for osteoporosis, researchers found that the ethanolic extract of CQ has bone-healing properties.

Recently, it was demonstrated that the petroleum ether extract of CQ enhances fetal bone growth and ossification.

Phytochemical analyses of CQ have revealed high contents of ascorbic acid, carotene, anabolic steroidal substances, and calcium. The stem contains 2 asymmetric tetracyclic triterpenoids and 2 steroidal principles. The presence of β-sitosterol, δ-amyrin, δ-amyrone, and flavanoids (quercetin) has also been reported. All of these components have potentially different metabolic and physiologic effects.

Although different uses of CQ have been investigated, the exact mechanism of its bone-healing properties has not been evaluated. Therefore, the present study aimed to evaluate the effects of petroleum ether extract of CQ on bone marrow MSC proliferation and osteogenic differentiation.

Materials and Methods

Plant extract

The stems of CQ were collected from the Nalgonda District of Andhra Pradesh, India, and identified and
authenticated by a botanist. A voucher specimen was deposited in the Pharmacology Department of the Manipal University (Manipal, Karnataka, India). The fleshy stems (2.5 kg) were washed, cut into small pieces, air-dried, and crushed into powder. Stem powder was exhaustively extracted with 95% ethanol using a Soxhlet apparatus, and a yield of 225 g was obtained. The total ethanol extract was concentrated in a vacuum, after which the extract was dissolved in water and the solution was partitioned using petroleum ether. A total of 18.2 g of petroleum ether extract was obtained.

**Animals**

Three-month-old male Wistar rats weighing approximately 225 g (n = 30) were housed in the Central Animal Research Facility of the Manipal University. These rats were housed in sanitized polypropylene cages containing sterile paddy husks as bedding. The animals were maintained under controlled temperature (23 ± 2°C) and humid (50 ± 5%) conditions with a 12-h light–dark cycle. All animals were allowed free access to distilled water and commercial diet. These rats were anesthetized with ether. Three male Wistar rats of the albino strain were anesthetized with ether.

**Primary cell culture and differentiation**

The isolated bone marrow MSCs were cultured in 6-well Corning polystyrene cell culture plates (50,000 cells/well for staining purposes and 10,000 cells/well for the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide [MTT] assay), in 2 different culture media: basal medium (BM; DMEM with 1% fetal bovine serum, 10 mM sodium pyruvate, 1 µM dexamethasone, 100 U/mL penicillin, and 100 µg/mL streptomycin) and osteogenic medium (OM; DMEM with 1% fetal bovine serum, 1 µM dexamethasone, 10 mM glycerol phosphate, 0.05 mM ascorbic acid, 100 U/mL penicillin, and 100 µg/mL streptomycin). Cells were incubated at 37°C in a 5% CO₂ atmosphere for 1 week with regular changes of media. Once monolayer cells were confluent, they were trypsinized and subcultured as required. Cells grown in either BMs or OM were treated with different doses of CQ extract (100, 200, and 300 µg/mL) for up to 28 days. The treated/untreated cells were then subjected to alkaline phosphatase (ALP), von Kossa staining, and MTT assays.

**Histochemical localization of alkaline phosphatase**

About 50,000 MSCs were plated in 6-well dishes. The MSCs were washed twice with phosphate-buffered saline (PBS) and fixed with 4% paraformaldehyde at 4°C for 30 min. After fixation, cells were washed 3 times with distilled water and then air-dried for 10 min. The cells were then stained with ALP for 30 min with fresh naphthol AS-MX phosphatase solution (0.2 g/L) containing fast red violet B salt (0.42 g/L) in 100 mM Tris-HCl (pH 0.9) at room temperature. ALP-positive cells were stained pink.

**von Kossa staining**

Cells were rinsed with PBS and fixed in 4% paraformaldehyde for 30 min. The cells were then washed with distilled water, treated with 2.5% sodium thiosulfate for 5 min, washed again with distilled water, and counterstained with methyl green. The calcified extracellular matrix appeared as black nodules.

**Cell proliferation assay**

The MSCs were seeded in four 96-well plates at a density of 1x10⁴ cells/well. These cells were grown either in control media (CMs)/BMs or in OMs. Both groups of cells were treated with 300 µg/mL petroleum ether extract of CQ for 48 h. After incubation, 20 μL of MTT stock solution was added to each well and incubated for 4 h at 37°C. Then, the formazan crystals were dissolved in dimethyl sulfoxide for 1 h at room temperature. The absorbance of the colored solution was measured using an enzyme-linked immunosorbent assay plate reader at a wavelength of 570 nm. Data were analyzed using the Student’s t-test.
in GraphPad. The represented data are the average values of 3 different assays. The growth rate of the control (Figure 1A, CM=bone marrow MSCs grown in BMs) cells was determined and set as 100%. The growth rates of cells grown in BMs and treated with CQ (CM + CQ), cells grown in OMs, and cells grown in OMs and treated with plant extract (OM + CQ) were compared to that of the control group (CM).

Results

CQ extract increases the proliferation rate of undifferentiated MSCs

The addition of 300 µg/mL petroleum ether extract of CQ to undifferentiated MSCs increased their proliferation rate significantly (by 2-fold) in comparison with that of cells grown in BMs alone (Figure 1A, P < .01). The proliferation rate of MSCs cultured in BMs with CQ extract was the same as that of MSCs grown in OMs alone (compare Figures 1A and 1B). Furthermore, treatment of the MSCs grown in OMs with plant extract resulted in a 3-fold increase in the cell proliferation rate in comparison with cells grown in BMs alone (Figure 1B). Thus, our results from 3 independent assays show that treatment of undifferentiated MSCs with the plant extract alone has a significant influence on proliferation, while an additive effect was seen when cells were also treated with OMs.

CQ extract induces differentiation of MSCs into osteoblasts

MSCs grown in BMs (DMEM) did not differentiate into osteoblasts and did not show ALP activity even after 28 days. Interestingly, MSCs grown in BMs and supplemented with CQ extract differentiated into osteoblasts, as identified by ALP activity. Mesenchymal cells cultured in BMs containing 100 µg/mL CQ extract were weakly positive for ALP activity, while cells cultured in media containing 200 µg/mL or 300 µg/mL CQ extract showed a dose-dependent increase in ALP activity. Furthermore, MSCs grown in BMs with different concentrations of CQ extract began to show ALP activity by the 15th day of treatment; most cells were strongly positive for ALP by the end of the 20th day of treatment. It has been shown that untreated MSCs must be cultured in OMs for 28 days before ALP-positive, differentiated osteoblasts can be identified. However, our results showed a dose-dependent increase in ALP activity in cells grown in OMs with 100, 200, and 300 µg/mL of CQ extract, as compared to the MSCs grown in OMs alone, beginning at the 7th day of the treatment. By the 15th day of CQ treatment in OMs, more than 95% of the cells were positive for ALP. Thus, CQ extract alone can differentiate MSCs into ALP-positive osteoblast cells, and can also accelerate the osteoblast differentiation process of MSCs in OMs in an additive fashion.

Effect of CQ extract on the mineralization of extracellular matrix

MSCs grown in BMs alone did not show any signs of mineralization in the extracellular matrix even after 28 days. However, MSCs grown in the BMs and treated with CQ extract (300 µg/mL) showed calcium deposition in the extracellular matrix by as early as 15 days after the beginning of the treatment. The MSCs cultured in the OMs alone showed mineralization after 28 days. Furthermore, cells treated with OMs supplemented with CQ extract (300 µg/mL) showed a greater extent of mineralization that was evident by as early as the 7th day. Thus, our result suggests that CQ extract not only induces the differentiation of MSCs into osteoblasts, but also causes the differentiated osteoblasts to deposit calcium salts in the extracellular matrix. Additionally, undifferentiated MSCs can be differentiated into functional osteoblasts by treatment with CQ extract alone, without any other stimulator in the culture media.
Discussion

Human bone consists of a mineralized organic matrix and bone cells. Osteoblasts are active mature bone cells that synthesize the organic matrix and regulate the mineralization process. Osteogenesis begins with osteoblast formation and secretion of type I collagen that makes up about 90% of the organic bone matrix, or the osteoid. Once osteoblasts are active, they begin to produce large amounts of ALP, a phosphate-splitting enzyme that is released into the osteoid to initiate the deposition of minerals. Calcium hydroxyapatite, which comprises 70% of the bone mass, crystallizes along the cavities in the 3-dimensional collagen network. After mineralization, the complete bone becomes hard and rigid with the mechanical properties necessary to withstand external forces, support the body, and protect the internal organs. The proliferation rate and biological activity of the osteoblasts control the rate of bone formation, while accelerated osteoblast growth is the key factor for efficient bone repair. The reduction in bone mass in osteoporosis is due to an imbalance between bone resorption and bone formation in which the rate of resorption exceeds that of formation. The most important risk factor for osteoporosis is advanced age, in both men and women. In women, estrogen deficiency after menopause is correlated with a rapid reduction in bone mineral density (BMD). In men, a decrease in testosterone levels has similar but less pronounced effects. Other causes of osteoporosis include tobacco-smoking, low body mass index, malnutrition, alcoholism, insufficient physical activity, and exposure to heavy metals such as cadmium.

Bone marrow MSCs are the source of bone-forming osteoblasts. The results of our experiments show that the petroleum ether extract of CQ can stimulate the differentiation of MSCs into osteoblasts in a dose-dependent manner even in the absence of osteogenic conditioning media. This activity of the plant extract is increased further in the presence of OMs. The plant extract also facilitated extracellular matrix mineralization that was more pronounced in the presence of OMs. Finally, the presence of plant extract in the control and OMs stimulated the proliferation rate of MSCs.

Results of this study clearly show that the CQ plant extract enhances the proliferation and differentiation ability of MSCs into osteoblasts. ALP activity, the most widely recognized biomarker for osteoblast activity, was enhanced by a short treatment with CQ. Findings of this study are in line with several previous in-vivo experiments that have demonstrated that CQ promotes ALP activity and enhances collagen synthesis in the fracture-healing process. In addition, this study also suggests that the petroleum ether fraction may contain active constituents that stimulate osteoblast differentiation and its bioactivity. The phyogenic steroids found in CQ7 may be involved in stimulating osteoblastogenesis and may act on estrogen receptors of bone cells.

The exact molecular mechanism involved in CQ-promoted osteogenesis remains to be explored. However, some evidence suggests that Wnt signaling may be involved. This pathway has been shown to play a significant role in the control of osteoblastogenesis and bone formation. Mutations in these signaling molecules are strongly associated with changes in BMD and fractures. Loss-of-function mutations in low-density lipoprotein receptor-related protein (LRP5) receptors cause osteoporosis–pseudoglioma syndrome, while gain-of-function mutations in the same group lead to high bone mass phenotypes. Using knockout and transgenic mouse models for Wnt pathway components, it has been established that this signaling pathway regulates many aspects of osteoblast physiology including commitment, differentiation, bone matrix formation/mineralization, and apoptosis as well as its coupling with osteoclastogenesis and bone resorption. Therefore, it is reasonable to suggest that the active constituents of CQ may stimulate the proliferation and differentiation of MSCs and promote new bone formation through the Wnt-LRP5-β-catenin signaling pathway for pre-osteoblast formation. Furthermore, the role of CQ in receptor activator of κB–receptor activator of κB ligand expression and osteoclast differentiation and activity needs to be identified. Recently, it has been shown that the CQ-mediated increase in osteoblast activity may be mediated through a mitogen-activated protein kinase-dependent pathway.

In-vitro and in-vivo data of this study suggest that CQ can be effectively used to treat various bone disorders and can also be used as a preventive measure for disorders that lead to decreased BMD.
Clinical Practice Pearls

Nutrition and the Healthy Heart with an Exercise Boost

Whayne TF Jr, Maulik N


In this era of potent medications and major cardiovascular (CV) procedures, the value of nutrition can be forgotten. A healthy diet is essential, regardless of CV risk. Caloric balance is inherent to a good diet. Despite patients who say they eat little, ideal weight can be maintained if calories are burned. Composition is another component of healthy diet. The Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets provide proof of CV benefit from their specific content. Metabolic syndrome (MS) is associated with poor diet and obesity. A healthy diet with good nutrition benefits MS patient with associated conditions such as obesity and diabetes. Exercise, in conjunction with a healthy diet and good nutrition, helps maintain optimal weight and provides CV benefits such as decreased inflammation and increased vasodilatation. Importance of vitamins or other nutritional supplements in a healthy diet is unproven. Nevertheless, the most promising data of added benefit to a healthy diet is with vitamin D. Some dietary supplements also have promise. Alcohol, in moderation, especially red wine, has nutritional and heart protective benefits. Antioxidants, endogenous or exogenous, have received increased interest and appear to play a favorable nutritional role. CV health starts with good nutrition.

Prevalence of Thoracic Vertebral Fractures in Hospitalized Elderly Patients with Heart Failure

Mazziotti G, et al


A cross-sectional study was conducted to evaluate the prevalence and determinants of radiological thoracic vertebral fractures in patients with heart failure (HF). A quantitative morphometric analysis was carried out in a total of 1031 elderly hospitalized patients (491 females and 540 males; median age: 75 years, range: 65–90; 430 patients with HF) for the presence of thoracic vertebral fractures using chest radiograph, routinely performed in the diagnostic work-up of HF.

Vertebral fractures were found in 166 patients (16.1%), the prevalence being significantly higher in patients with HF as compared with those without HF, either in females (30.9% vs. 15.8%; \( P < .001 \)) or in males (16.4% vs. 7.4%; \( P = .001 \)). The association between HF and vertebral fractures remained statistically significant (odds ratio: 2.14, 95% confidence interval: 1.25–3.66; \( P = .01 \)) even after adjustment for age, sex, loop diuretic therapy, anticoagulant therapy, proton pump therapy, coexistent chronic obstructive pulmonary disease, diabetes mellitus, renal insufficiency, and chronic liver diseases. In patients with HF, vertebral fractures were positively correlated with female sex, duration of HF, ischemic heart disease, cigarette smoking, and treatment with anti-osteoporotic drugs; and inversely correlated with left ventricular ejection fraction.

Hospitalized patients suffering from HF are at a higher risk of vertebral fractures than patients without HF in the same clinical context.
Dermatology

Physical Activity and Dark Skin Tone: Protective Factors Against Low-bone Mass in Mexican Men

Vivanco-Muñoz N, et al


A cross-sectional study was conducted on 268 Mexican males aged between 13 and 80 years to evaluate the association of clinical factors related with bone mass. Male individuals from high schools, universities, and retirement homes were invited to participate. Body mass index (BMI) was measured and bone mineral density (BMD) was assessed using dual-energy X-ray absorptiometry for L1–L4 and total hip. Factors related to bone mass were assessed and analyzed using a questionnaire and a logistic regression model, respectively. Demographic factors (age, education, and occupation), clinical data (BMI, skin tone, previous fracture, history of osteoporosis [OP], and history of fractures), and lifestyle variables (diet, physical activity, sun exposure, and smoking) were also evaluated. Physical activity (≥ 60 min/5 times a week) reduced the risk for low BMD as regards age, osteopenia, and OP at the spine and total hip (odds ratio [OR]: 0.276; 95% confidence interval [CI]: 0.099–0.769; *P* = .014; and OR: 0.184; 95% CI: 0.04–0.849; *P* = .03, respectively). Therefore, in this population of healthy Mexican males (aged 13–80 years), it was observed that dark skin (showed 70% decrease in the risk of low-bone mass) and physical activity were protective factors against low-bone mass.

Effect of Glycemic Index of Carbohydrates on Acne Vulgaris

Reynolds RC, et al


Acne vulgaris may be improved by dietary factors that increase insulin sensitivity. It was hypothesized that a low-glycemic index diet would improve facial acne severity and insulin sensitivity. Fifty-eight adolescent males (mean age ± standard deviation: 16.5 ± 1.0 years and body mass index: 23.1 ± 3.5 kg/m²) were alternately allocated to high or low glycemic index diet. Severity of inflammatory lesions on the face, insulin sensitivity (homeostasis modeling assessment of insulin resistance), androgens, and insulin-like growth factor-1 and its binding proteins were assessed at baseline and at 8 weeks, a period corresponding to the school term. Forty-three individuals (*n* = 23, low glycemic index and *n* = 20, high glycemic index) completed the study. Diets differed significantly in glycemic index (mean ± standard error of the mean, low glycemic index: 51 ± 1 vs. high glycemic index: 61 ± 2, *P* = .0002), but not in macronutrient distribution or fiber content. Facial acne improved on both diets (low glycemic index: -26 ± 6%, *P* = .0004 and high glycemic index: -16 ± 7%, *P* = .01), but no significant differences were observed between the diets. Change in insulin sensitivity was not different between diets (low glycemic index: -0.2 ± 0.1 and high glycemic index: 0.1 ± 0.1, *P* = .60) and did not correlate with change in acne severity (Pearson correlation, *r* = -0.196, *P* = 0.244). Longer time frames, greater reductions in glycemic load, or/and weight loss may be necessary to detect improvements in acne among adolescent boys.
Osteopenic bone disease occurs frequently among patients with chronic liver disease, but has not been well studied in those with primary sclerosing cholangitis (PSC). In the present study, the prevalence, rate of progression, and independent predictors of bone disease were investigated in a large number of patients with all stages of PSC. Bone mineral density of the lumbar spine, hip, and total body was measured yearly for 10 years in 237 patients with PSC. Osteoporosis (T-score < -2.5) was found in 15% of patients and occurred 23.8-fold (95% confidence interval [CI]: 4.6–122.8) more frequently in those with PSC than expected from a matched population. By multivariate analysis, age (54 years or older, odds ratio [OR]: 7.8; 95% CI: 3.3–18.3), body mass index (≤ 24 kg/m², OR: 4.9; 95% CI: 1.9–12.6), and inflammatory bowel disease for individuals older than or equal to 19 years (OR: 3.6; 95% CI: 1.5–8.4) were correlated with the presence of osteoporosis. It was observed that osteoporosis was present in 75% of patients with all 3 risk factors but in only 3.1% of those without all of them. Patients with PSC lost 1% of bone mass per year; this rate of bone loss was significantly associated with duration of inflammatory bowel disease.

Osteoporosis occurs frequently among patients with PSC. Old age, low body mass index, and long duration of inflammatory bowel disease can be used to identify patients with PSC who might derive the most benefit from measurements of bone density and treatments for bone diseases.

The prevalence of low-trauma fracture in CP patients is comparable with or higher than that of “high-risk” GI illnesses, for which osteoporosis screening guidelines exist.
Gynecology

Alcohol Consumption and Bone Mineral Density in Elderly Women

Sommer I, et al

Findings with regard to alcohol consumption and bone mineral density (BMD) in elderly women have been inconsistent. The objective of the present study was to explore the association of alcohol intake with BMD in elderly women.

This cohort study included women from the population-based Kuopio Osteoporosis Risk Factor and Prevention - Fracture Prevention Study (OSTPRE - FPS). Alcohol intake and potential confounders were assessed at baseline and after 3 years of follow-up using a lifestyle questionnaire. In addition, a Food Frequency Questionnaire (FFQ) was distributed in the third year to measure dietary intake, including alcohol. Women underwent BMD measurements at the femoral neck and lumbar spine at baseline and after 3 years of follow-up.

Three hundred elderly women (mean age: 67.8 years) from Kuopio Province, Finland, provided both BMD measurements and FFQ data.

Alcohol consumption estimated from the FFQ and lifestyle questionnaires was significantly associated with BMD at both measurement sites after adjustment for potential confounders, including lifestyle and dietary factors ($P < .05$). Using the FFQ, women drinking more than 3 alcoholic drinks per week had significantly higher BMD than abstainers, 12.0% at the femoral neck, and 9.2% at the lumbar spine. Results based on the lifestyle questionnaire showed higher BMD values for all alcohol-consuming women at the femoral neck and for women drinking 1 to 3 alcoholic beverages per week at the lumbar spine, compared with nonusers.

Results from OSTPRE - FPS suggest that low-to-moderate alcohol intake may exert protective effects on bone health in elderly women.

Asthma and Menopause: A Systematic Review and Meta-analysis

Zemp E, et al

The objective of this study was to review the available literature and to determine if the menopausal transition is associated with asthma incidence. A systematic review and meta-analysis of cohort and cross-sectional studies providing a definition/assessment of menopausal status, an incidence or prevalence of a defined diagnosis of asthma, and a measure of the association or of menopausal state and asthma or enough data for a calculation of this association were conducted. Where possible, these meta-analytic estimates were also stratified by intake of menopausal hormone therapy (MHT).

Of the 76 potentially relevant articles, 8 studies met the inclusion criteria and were included in the review while 6 were included in the meta-analysis. There was heterogeneity across studies: 4 studies reported slightly increased prevalence rates of asthma in postmenopause, 1 large cohort yielded a lower asthma incidence, and 1 cross-sectional study a lower prevalence in post-menopause. Overall, the meta-analysis showed no significant association between menopause and asthma rates. When stratifying by use of MHT, the association between menopause and asthma rates was increased in women reporting use of MHT (relative risk: 1.32, 95% confidence interval: 1.01–1.74), than in women not using MHT.

No significant association of menopause with asthma prevalence or incidence was observed, except for women reporting use of MHT. Further studies addressing subgroup analyses more closely as well as a possible modification of the association of menopause and asthma by MHT are needed.
A Novel Appetite Peptide, Nesfatin-1 in Patients with Nonalcoholic Fatty Liver Disease

Başar O, et al

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver pathologies worldwide and is strongly associated with obesity, insulin-resistance, and food intake. Nesfatin-1 is a new peptide that controls appetite and food intake. The objective of this research was to examine the serum concentrations of nesfatin-1 in NAFLD.

Thirty patients with NAFLD, who had elevated liver enzymes, aged 40 years were included in this study along with sex-matched healthy individuals. NAFLD was diagnosed and graded with the findings of liver ultrasound scan. Nesfatin-1 concentrations were measured using ELISA method, and the relationship between nesfatin-1 and metabolic parameters was investigated. The individuals were divided into 2 groups according to their body mass index (≥ 30 and < 30), and nesfatin-1 concentrations were examined between both groups. Serum nesfatin-1 concentrations in patients with NAFLD were lower than that of healthy controls (0.26 ± 0.14 ng/mL, 0.38 ± 0.18 ng/mL, respectively; \( \text{P} = .008 \)). A negative correlation was observed between nesfatin-1 and fasting glucose and body mass index. In obese individuals, serum nesfatin-1 concentrations were significantly lower when compared with nonobese individuals (0.26 ± 0.12 ng/mL, 0.37 ± 0.19 ng/mL, respectively; \( \text{P} = .014 \)). In addition, we showed that nesfatin-1 concentrations in individuals with insulin resistance were significantly lower in comparison with insulin-sensitive ones (0.27 ± 0.17 ng/mL, 0.38 ± 0.17 ng/mL, respectively; \( \text{P} = .015 \)).

This study showed that nesfatin-1 concentrations were reduced in NAFLD, thus indicating that nesfatin-1 may have a significant role in NAFLD.

Is Liver Transplantation Associated with Decreased Bone Mass in Climacteric Women?

Baccaro LF, et al

The present study was conducted to evaluate whether climacteric women undergoing liver transplantation had higher prevalence of decreased bone mass than those without any liver disease. A cross-sectional study in which 48 women received follow-up care at a university hospital in Southeastern Brazil, from February 4, 2009 to January 5, 2011, was conducted. Of all these women, 24 were of older than or equal to 35 years and had undergone liver transplantation at least 1 year before study entry. The remaining 24 women had no liver disease and their age and menstrual patterns were similar to those of transplanted patients. Laboratory tests (follicle-stimulating hormone and estradiol) and bone density measurements of the lumbar spine and femur (equipment: Hologic - Discovery Wi, Bedford, Massachusetts, USA) were performed. Statistical analysis was carried out using Fisher’s exact test, simple odds ratio (OR), and multiple logistic regression.

Mean age of women included in the study was 52.8 (±10.7) years; 27.1% were premenopausal and 72.9% were peri/postmenopausal. Approximately, 14.6% of these women exhibited osteoporosis and 35.4% had low bone mass. The following items were associated with decreased bone mass: being postmenopausal (OR: 71.4; 95% confidence interval [CI]: 3.8–1339.7; \( \text{P} < .0001 \)), current age > 49 years (OR: 11.4; 95% CI: 2.9–44.0; \( \text{P} = .0002 \)), and serum estradiol levels lower than 44.5 pg/mL (OR: 18.3; 95% CI: 3.4–97.0; \( \text{P} < .0001 \)). Presence of a history of liver transplantation was not associated with decreased bone mass (OR: 1.4; 95% CI: 0.4–4.3; \( \text{P} = .56 \)).

Liver transplantation was not associated with decreased bone mass in this group of climacteric women.
Infections

Bone Alterations in Hepatitis C Virus-infected Patients

Pelazas-González R, et al


Most studies have shown that patients with chronic hepatitis C virus (HCV) infection are affected by osteoporosis. However, liver function impairment and deranged nutrition may both play a role in the observed bone alterations. In some studies, no osteoporosis was found, while in others cases of osteosclerosis have been reported. The aim of the present study was to assess bone alterations in treatment-naive, well-nourished, HCV patients, in order to discern whether or not HCV infection causes osteoporosis.

Whole-body bone densitometry and assessment of T-score at lumbar spine and hip were performed in 40 patients and 40 age-matched and sex-matched controls, with a Lunar Prodigy Advance (General Electric, Piscataway, New Jersey, USA). All the patients underwent liver biopsy. Nutritional evaluation was made by subjective nutritional assessment, body mass index (BMI), and densitometric assessment of total lean mass and total fat mass. Serum osteocalcin, osteoprotegerin, receptor activator of nuclear factor κB ligand (RANKL), parathyroid hormone (PTH), crosslaps, vitamin D3, testosterone, insulin-like growth factor (IGF-1), and estradiol were also determined.

Patients did not show any differences in total bone mineral density (BMD) or T-score when compared with controls. In contrast, about one-third of them showed positive T-scores. Patients showed lower IGF-1, vitamin D3, and testosterone levels, but higher telopeptide and osteoprotegerin levels. Multivariate analyses disclosed that age, sex, and total lean mass were the only parameters that were independently related to BMD. Therefore, chronic HCV infection in well-nourished patients with preserved liver function does not cause osteoporosis.

Osteoporosis and Bone Health in HIV patients

Powderly WG


Patients with HIV can develop several complications that involve bone, including low bone mineral density and osteoporosis, osteonecrosis, and rarely osteomalacia. Low bone mineral density leading to osteoporosis is the most common bone pathology. It may result from HIV infection (directly or indirectly), antiretroviral toxicity, or as a consequence of other co-morbidities. The clinical relevance of osteoporosis in HIV infection has been uncertain; however, fragility fractures are increasingly reported in HIV-infected patients. Further research is required to understand the pathogenesis of osteoporosis in HIV-infected patients and to determine effective management.

However, initiation of antiretroviral therapy seems to accelerate (in the short-term) bone demineralization. Tenofovir may be associated with a greater degree of short-term loss of bone density than other antiviral agents, while the potential long-term bone dysfunction is unclear. As the HIV-infected population ages, screening for low bone mineral density will become increasingly important.
Nutrition and the Risk of Stroke

Hankey GJ


Poor nutrition in the first year of a mother’s life, and undernutrition in utero, infancy, childhood, and adulthood predispose individuals to stroke in later life, but the mechanism of increased stroke risk is unclear. Overnutrition also increases the risk of stroke, probably by accelerating the development of obesity, hypertension, hyperlipidemia, and diabetes.

Reliable evidence suggests that dietary supplementation with antioxidant vitamins, B vitamins, and calcium does not reduce the risk of stroke.

Less reliable evidence suggests that stroke can be prevented through diets that are prudent, aligned to the Mediterranean or Dietary Approaches to Stop Hypertension (DASH) diets, low in salt and added sugars, high in potassium, and meet, but do not exceed, energy requirements. Trials in progress are examining the effects of vitamin D and marine omega-3 fatty acid supplementation on incidence of stroke. Future challenges include the need to improve the quality of evidence linking many nutrients, foods, and dietary patterns to the risk of stroke.

Incidence of Major and Minor Brain Injuries in Facial Fractures

Grant AL, et al


Facial fractures can be associated with brain and cervical spine injuries as impact forces are transmitted through the head and neck. Although major brain injury is commonly recognized in these patients, incidence of minor brain injury is not well-known, despite potential morbidity and mortality.

This prospective study aimed to determine the incidence of both major and minor brain injuries in 100 patients presenting to a craniofacial surgery service with facial fractures and to identify characteristics associated with brain injury. Data were collected for a 9-month period by a craniofacial surgeon at a level I trauma center. A questionnaire and checklist were designed to capture information about major and minor brain injuries in patients with facial fractures. Assessments were completed in the outpatient clinic, emergency department, hospital ward, or intensive care unit during the first patient encounter.

The average age of patients was 34 years; 79% were males. Time between injury and assessment ranged from less than a few hours to 4 months. Incidence of brain injury was 67% overall: 29% with major brain injury and 38% with minor brain injury. Major brain injury was commonly diagnosed early in the emergency department or intensive care unit. Conversely, minor brain injury tended to be diagnosed late in the clinic. Patient age, mechanism of injury, and type of facial fracture predicted brain injuries overall, but mechanism of injury was the sole predictor of minor brain injury.
Ophthalmology

The Burden Associated with Ocular Symptoms in Allergic Rhinitis

Klossek JM, et al


Ocular symptoms remain widely neglected while they concern the majority of individuals with allergic rhinitis (AR) and impair their daily activities. In the present study, characteristics of ocular symptoms in individuals suffering from AR in the French INSTANT study and their impact on daily activities are described.

A cross-sectional observational survey was carried out in November 2006 through face-to-face interviews. About 31.7% of the population-based sample ($n = 4019$) suffered from AR, whereas 52.0% of AR individuals ($n = 663$) described ocular symptoms. Men had significantly less ocular symptoms than women (odds ratio: 0.71, 95% confidence interval: 0.57–0.89). It was observed that 57.5% of individuals suffered from ocular symptoms for more than 5 years, 30.2% for more than 6 months in the past 12 months, and 92.2% during the pollen season. The troublesome ocular symptoms included itching eyes (51.1%), watery eyes (38.6%), red eyes (6.6%), and swollen eyelids (3.6%). The trigger factors were pollens (51.3%), household dust and mites (34.8%), pets (12.2%), and air pollution (3.8%). Ocular symptoms had a negative impact on daily activities (blurred sight: 47.8%, reduction in daily activities: 38.8%, reduced efficacy at work: 25.8%, sleep disturbances: 16.3%, and sick leave: 12.9%). They were diagnosed in 38.9% individuals and followed in 34.8% individuals. Treatment for ocular symptoms was prescribed to 35.4% individuals and to 61.9% individuals with a regular follow-up care.

This survey confirms the impact of ocular symptoms on AR patients’ lives and suggests that they are still neglected and undertreated.

Ophthalmic Manifestations of Atypical Immunoglobulin D Multiple Myeloma

Edmunds MR, et al

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A previously healthy 32-year-old Caucasian female presented with sudden-onset horizontal diplopia after a paroxysm of coughing. She had recently sustained a pubic ramus fracture during an innocuous fall, and had also noted a firm lump developing at the right side of her forehead. On examination, she had a right frontotemporal mass. Visual acuities were 6/6 bilaterally. There was reduced abduction of the right eye, bilateral white, granular corneal opacities, and evidence of bilateral optic disc swelling. Hematological investigations revealed normocytic anemia, hypercalcemia, and raised erythrocyte sedimentation rate (ESR). Computed tomography showed lytic foci throughout the skull, ribs, scapulae, spine, pelvis, and upper femora. Serum protein electrophoresis revealed immunoglobulin D (IgD)-kappa paraproteinemia; urine electrophoresis showed free light chain kappa, and bone marrow biopsy demonstrated 87% plasma cells. A diagnosis of IgD multiple myeloma was made, with subsequent chemotherapeutic treatment and eventual autologous stem cell transplant that resulted in a resolution of neuro-ophthalmic manifestations and prolonged disease remission.
Orthopedics

Nutrition Education for Osteoporosis Prevention in Men with Prostate Cancer Initiating Androgen Deprivation Therapy

Millar H, Davison J


Osteoporosis is a common side effect of treatment with androgen deprivation therapy (ADT) in men with prostate cancer. ADT may prolong survival; however, deterioration of bone mass density occurs soon after initiation. A systematic review of current literature revealed the importance of adequate nutrition during treatment with ADT to reduce the risk of osteoporosis. More specifically, this literature stressed achieving adequate intake of calcium and vitamin D through a combination of supplements and food. The necessity of providing nutrition education to patients with prostate cancer at initiation of ADT was identified. Healthcare professionals, including nurses, oncologists, and dietitians, can be instrumental in identifying patients with prostate cancer initiating ADT who are at risk for osteoporosis. Research on nutrition and lifestyle modification interventions to maintain bone health and reduce fracture risk for patients initiating ADT is limited. Additional research is required to develop and evaluate nutrition education interventions that will reduce the risk and prevent osteoporosis in men on ADT.

Nutrition, Physical Activity, and Bone Mineral Density in Youth with Autistic Spectrum Disorders

Soden SE, et al


Fractures and pain, secondary to low bone mineral density (BMD), have been reported in pediatric patients with autistic spectrum disorders (ASDs). The purpose of this study was to assess the BMD of a clinical sample of children with ASD aged between 10 and 18 years, and the nutrition and physical activity correlates of skeletal health in this population.

Twenty-six children with ASD were recruited from an outpatient multidisciplinary child-development clinic. Lumbar bone density was measured using dual-energy x-ray absorptiometry. Data collection included anthropometries, serum nutrient levels, parent interview, and 72-h diet, screen-time, and physical activity records. Four patients (15%) met criteria for pediatric low BMD with z scores ≤ –2.0, whereas another 4 were at risk with z scores ≤ -1.0. Approximately, 54% of participants had insufficient serum 25-hydroxy vitamin D. Mean electronic media use was 251 min/day, while mean physical activity was 69 min/day. Less than 50% of participants met the daily reference intake of vitamins A, B3, D, E, K, zinc, calcium, folate, potassium, and fiber. Bone density correlated positively with body mass ($r = .47$), calcium intake ($r = .46$), and calorie intake ($r = .58$).

Children with ASD, aged between 10 and 18 years, are at risk for occult low bone density. In this study, children with low body mass index and insufficient calcium and calorie intakes were at greater risk. Other unhealthy behaviors in this population included a high screen-time to physical activity ratio and multiple nutrient deficiencies.
Pediatrics

Association of Maternal Diabetes and Child Asthma

Azad MB, et al


Perinatal programming is an emerging theory for the fetal origins of chronic disease. Maternal asthma and environmental tobacco smoke (ETS) are 2 of the best-known triggers for the perinatal programming of asthma, while the potential role of maternal diabetes has not been widely studied.

The objective of this study was to determine if maternal diabetes is associated with child asthma, and if so, whether it modifies the effects of ETS exposure and maternal asthma. A total of 3574 Canadian children, aged between 7 and 8 years, enrolled in a population-based birth cohort were studied. Standardized questionnaires were completed by the children’s parents, and data were analyzed by multivariable logistic regression.

Asthma was reported in 442 children (12.4%). Compared with those without asthma, asthmatic children were more likely to have mothers ($P = .003$), but not fathers ($P = .89$), with diabetes. Among children without maternal history of diabetes, the likelihood of child asthma was 1.4-fold higher in those exposed to ETS (adjusted odds ratio: 1.40; 95% confidence interval: 1.13–1.73), and 3.6-fold higher in those with maternal asthma (3.59; 2.71–4.76). Among children born to diabetic mothers, these risks were amplified to 5.7-fold (5.68; 1.18–27.37) and 11.3-fold (11.30; 2.26–56.38), respectively. In the absence of maternal asthma or ETS, maternal diabetes was not associated with child asthma (0.65, 0.16–2.56).

Our findings suggest that maternal diabetes may contribute to the perinatal programming of child asthma by amplifying the detrimental effects of ETS exposure and maternal asthma.

Cell-mediated Nonallergic Rhinitis in Children

Maselli Del Giudice A, et al


Nonallergic rhinitis is a heterogeneous disease whose etiology is largely unknown. The aim of this study was to define the incidence, clinical features, and comorbidity of the different types of cell-mediated nonallergic rhinitis in a pediatric-age group.

One hundred and fourteen nonallergic children with chronic nasal obstruction and associated symptoms (rhinorrhea, sneezing, and nasal itchiness) were, retrospectively, selected and had been submitted to a clinical history, pediatric evaluation, anterior rhinoscopy and fiberendoscopy, rhinomanometry, and nasal cytology. Nonallergic rhinitis with neutrophils was present in 46 (40.4%) children, nonallergic rhinitis with eosinophils in 53 (46.5%) children, nonallergic rhinitis with mast-cells in 12 (10.5%) children, and nonallergic rhinitis with both eosinophils and mast-cells in 3 (2.6%) children. Nasal obstruction was prevalent in nonallergic rhinitis with eosinophils and in nonallergic rhinitis with mast-cells ($P < .001$), whereas rhinorrhea and sneezing was prevalent in only the nonallergic rhinitis with eosinophils ($P < .0001$). On the other hand, nasal itching was prevalent in the nonallergic rhinitis with mast-cells ($P < .0003$). The nonallergic rhinitis with eosinophils group showed a higher probability of asthma ($P < .02$) and respiratory sleep disorders ($P < .04$).

In the pediatric-age group, the most frequent forms of nonallergic rhinitis are those with eosinophils or neutrophils. A diagnosis of nonallergic rhinitis with eosinophils in children presumes more severe symptoms and a higher incidence of pulmonary disease and rhinopathy.
Effect of Inhaled Glucocorticoids in Childhood on Adult Height

Kelly HW, et al


The use of inhaled glucocorticoids for persistent asthma causes a temporary reduction in growth velocity in prepubertal children. The resulting decrease in attained height 1 to 4 years after the initiation of inhaled glucocorticoids is considered to be non-influential on the attained adult height. We measured adult height in 943 of 1041 participants (90.6%) in the Childhood Asthma Management Program; adult height was determined at a mean (±SD) age of 24.9 ± 2.7 years. Starting at the age of 5 to 13 years, the participants had been randomly assigned to receive 400 µg of budesonide, 16 mg of nedocromil, or placebo daily for 4 to 6 years. We calculated differences in adult height for each active treatment group, as compared with the placebo.

Mean adult height was 1.2 cm lower (95% confidence interval [CI], -1.9 to -0.5) in the budesonide group than in the placebo group (*P* = .001) and was 0.2 cm lower (95% CI, -0.9 to 0.5) in the nedocromil group than in the placebo group (*P* = .61). A larger daily dose of inhaled glucocorticoid in the first 2 years was associated with a lower adult height (-0.1 cm for each µg per kg body weight) (*P* = .007). The reduction in adult height in the budesonide group as compared with the placebo group was similar to that seen after 2 years of treatment (-1.3 cm; 95% CI, -1.7 to -0.9). The initial decrease in attained height associated with the use of inhaled glucocorticoids in prepubertal children persisted as a reduction in adult height, although the decrease was not progressive or cumulative.

Bone Effects of Rosiglitazone in HIV-infected Patients with Lipoatrophy

Ross AC, et al


Thiazolidinediones increase limb fat in HIV positive patients with lipoatrophy. However, their use in the general population has been associated with bone loss and fracture. We sought to determine the effects of rosiglitazone on bone metabolism in HIV-infected patients.

HIV positive patients with lipoatrophy were randomized to rosiglitazone versus placebo for 48 weeks in a double-blind, placebo-controlled trial. Limb fat, bone mineral density (BMD), bone formation markers (procollagen type 1 amino-terminal propeptide [P1NP], osteocalcin [OC]) and bone resorption markers (C-terminal telopeptide of type I collagen [CTX]) were measured, along with receptor activator for nuclear factor kappa-β ligand (RANKL), osteoprotegerin (OPG), and inflammatory cytokines.

Seventy-one subjects were randomized to rosiglitazone or placebo; total BMD did not change significantly in either group. In the rosiglitazone group, P1NP showed statistically significant decreases at 24 and 48 weeks; however, compared with the placebo changes were only significant at 24 weeks. OC decreased significantly in the rosiglitazone group at 24 weeks, but there were no between-group differences. CTX, RANKL, or OPG did not change for either group. Multivariable regression within the rosiglitazone arm showed P1NP changes were inversely associated with limb fat changes, protease inhibitors, and tenofovir use.

Rosciglitazone use was associated with decreased bone formation, but it did not alter bone resorption or total BMD. The increase in limb fat that accompanies rosiglitazone use appears to be associated with decreased osteoblast activity. Further studies are needed to determine the effect of thiazolidinediones on bone health in HIV-infected persons.
Bilateral Subcapital Femoral Neck Fractures Secondary to Transient Osteoporosis During Pregnancy: A Case Report

Emami MJ, et al


Abstract

Transient osteoporosis during pregnancy is a rare, self-limiting disease. The authors report a case of a 36-year-old woman who had bilateral subcapital femoral neck fractures during the 6th month of pregnancy. The diagnosis was made 4 days after delivery, because radiography was declined by the patient for fear of radiation effects. Fixation was not feasible owing to bone resorption, and 2-stage bipolar hemiarthroplasty was therefore performed. Magnetic resonance imaging (MRI) is the best non-invasive investigative tool for pregnant women with hip pain. Early detection can prevent complications and resorting to major surgeries.

Key Words: Femoral neck fractures, osteoporosis, pregnancy

Introduction

Transient osteoporosis is a rare, self-limiting, idiopathic skeletal disease presenting as loss of bone density and thinning of the cortex. It usually affects middle-aged men, women in the third trimester of pregnancy, and primiparous women just after delivery. The most common site involved is the hip (particularly on the left side); other sites include the vertebra, talus, knee, and acetabulum. Twenty-five percent to 30% of the patients have bilateral hip involvement. Femoral neck fractures usually occur 2 months after the onset of symptoms, when bone mass is at its lowest level.

Case Report

A 36-year-old primiparous woman presented with acute bilateral groin and hip pain aggravated by walking during the 6th month of twin pregnancy. Her pregnancy was a result of in vitro fertilization. She had been infertile for about 15 years. Radiography was declined by the patient due to concerns regarding dangers of ionizing radiation. She was then prescribed acetaminophen and advised bed rest. Four days after delivery by cesarean section, she presented again with painful hips. Radiographs showed bilaterally displaced subcapital femoral neck fractures. CT and MRI showed lower bone density in the femoral heads than in the proximal femurs as well as bone resorption indicating old fractures. Whole body bone scan showed increased uptake in both femoral necks and excluded bony metastasis. Bone densitometry indicated osteoporosis in the hips and spine.

The patient was prescribed unfractionated heparin by an obstetrician; and there was no history of any thyroid, parathyroid, metabolic, or bowel diseases. Blood tests for calcium, phosphate, 24-h urine calcium, and creatine excretion; function tests for liver, thyroid, and kidney; blood cell count, complement (C3, C4), antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody–perinuclear (ANCA-P) and anti-neutrophil cytoplasmic antibody-cytoplasmic (ANCA-C), anti-dsDNA, purified protein derivative (PPD) test; and brucella antibody test were all within normal range, except for the erythrocyte sedimentation rate (125 mm/h) and C-reactive protein (48 mg/L).

As the hip fractures were old, bones were displaced, and bone quality was poor, internal fixation was not feasible and hence a 2-stage bilateral bipolar modular hemiarthroplasty was performed. Early ambulation and rehabilitation was allowed. Pain subsided completely and full function achieved gradually. At the 2-year follow-up, she was well with acceptable function of both hips.
Transient demineralization during pregnancy was first reported about 50 years ago in 3 pregnant women. This condition is also known as transient osteoporosis, bone marrow edema syndrome, regional migratory osteoporosis, transient migratory osteoporosis, and hip algodystrophy. It occasionally affects lactating mothers and slender primiparous women in their third trimester of pregnancy. It usually affects one or both hips, either simultaneously or sequentially. Recurrence in later pregnancy has also been reported. Its risk factors include poor nutrition, low calcium intake, and family history of osteoporosis. The exact etiology is unknown; chemical, hormonal, mechanical and genetic factors, viral infection, and neurovascular theories have been proposed. The most accepted mechanism is microvascular injury, which leads to tissue ischemia and then marrow edema.

The course of transient osteoporosis is benign and patients eventually recover within 6–12 months. During the first phase (first 2 months), patient experiences hip pain and limping; radiographs will be normal, while diffuse edema is noted on MRI. In the second phase symptoms increase and radiographs show osteoporosis with normal joint space. Homologous focal lesions are specific MRI features. In the third phase (6-12 months), recovery and return to function can be expected with MRI findings gradually returning to normal.

Differential diagnosis includes pubis symphysiolysis, septic arthritis, malignancy, synovial disorders, reflex sympathetic dystrophy, and osteonecrosis. The pattern of pain in transient osteoporosis is of sudden onset and induced by weight bearing; and alleviated by rest. Pain characteristics in osteonecrosis are insidious in onset, continue at rest, and gradually increase without spontaneous recovery. The latter is most difficult to treat.

Radiography cannot help in the diagnosis of transient osteoporosis in the first phase; MRI is the best noninvasive investigative tool for pregnant women with hip pain, in whom arthralgia and musculoskeletal discomfort is often considered to be normal. MRI shows diffuse homogenous lesion without collapse in the proximal femur, which is hyperintense in T2-weighted images and hypointense in T1-weighted images. Early detection using MRI can prevent complications and major surgeries.
**Cissus quadrangularis**

**Sanskrit name/Indian name:** Hadjod

**English name:** Winged treebine

*Cissus quadrangularis* Facilitates Osteoblastogenesis

Potu BK, et al.


*Cissus quadrangularis*, commonly known as Hadjod, is widely used in traditional ayurvedic medicines. The aims of the present study were to evaluate the effects of petroleum ether extract of *C. quadrangularis* and the additive effect of osteogenic media and *C. quadrangularis* on the proliferation rate of bone marrow mesenchymal stem cells (MSCs), differentiation of marrow MSCs into osteoblasts (osteoblastogenesis), and calcification of extracellular matrix. MSCs were cultured in the media with or without *C. quadrangularis* extracts for 4 weeks and were then stained for alkaline phosphatase (ALP). Extracellular matrix calcification was confirmed by von Kossa staining. Marrow MSC cultures in control media and osteogenic media supplemented with *C. quadrangularis* extracts (100, 200, or 300 µg/mL) were also subjected to a cell proliferation assay.

Treatment with petroleum ether extracts of *C. quadrangularis* (100, 200, or 300 µg/mL) enhanced the differentiation of marrow MSCs into ALP-positive osteoblasts and increased extracellular matrix calcification. Treatment with 300 µg/mL petroleum ether extract of *C. quadrangularis* also enhanced the proliferation rate of the marrow MSCs. Cells grown in osteogenic media containing *C. quadrangularis* exhibited higher proliferation, differentiation, and calcification rates than did control cells. These results suggest that *C. quadrangularis* stimulates osteoblastogenesis, and can also be used as a preventive/alternative natural medicine in the treatment of bone diseases such as osteoporosis.

**Emblica officinalis, Terminalia bellirica, and Terminalia chebula**

**Sanskrit name/Indian name:** Triphala (Amalaki, Bibhitaki, and Haritaki)

**English name:** Indian gooseberry, Belleric myrobalan, and Chebulic myrobalan

Comparison of Enteroprotective Efficacy of Triphala on Methotrexate-induced Small Intestinal Damage in Rats

Nariya M, et al.


Triphala, categorized as a rejuvenator and antioxidant-rich ayurvedic herbal formulation, has been traditionally used in the treatment of various gastric problems, including intestinal inflammation. The aim of this study was to examine the comparative enteroprotective effect of Triphala against methotrexate (MTX)-induced intestinal damage in rats. Triphala formulations were prepared by mixing equal (1:1:1) and unequal (1:2:4) proportions of *Terminalia chebula* Retz., *Terminalia bellirica*, and *Emblica officinalis*. Intestinal damage was induced by administering MTX at a dose of 12 mg/kg, orally for 4 days to albino rats, and the response was assessed by gross and microscopic injury, measuring the intestinal permeability to phenol red, and tissue biochemical parameters. Equal and unequal formulations of Triphala at the dose of 540 mg/kg significantly restored the depleted protein level in brush border membrane of the intestine, phospholipid and glutathione contents, and decreased the myeloperoxidase and xanthine oxidase levels in the intestinal mucosa of MTX-treated rats. On the basis of these results, it can be concluded that unequal formulation of Triphala provides significantly more protection than equal formulation of Triphala against MTX-induced damage in rat intestine.
Eleusine coracana

Sanskrit name/Indian name: Nartaka
English name: Finger millet

Evaluation of Phenolic Content and Antioxidant Capacity of *Eleusine coracana* (L.)

Mehta JP, et al.

*Eleusine coracana* (native to east African highland, India, and China) is considered as one of the richest sources of phenolics and flavonoids, which have high biological activity. There are many factors such as surrounding atmosphere, environmental conditions, and soil conditions, which affect the phenolics and their antioxidant capacity. The present study deals with the separation and identification of the minor anti-oxidative components found in *E coracana* (L.). These components were detected and separated using semi-preparative-high performance liquid chromatography-photo diode array (HPLC-PDA) technique followed by gas chromatography-mass spectrometry (GC-MS) for their characterization.

*E coracana* (L.) samples were preserved in a dark and dry place at ambient temperature with passive ventilation prior to extraction. The phenolics of *E coracana* (L.) were extracted successively with the help of 1% acidified methanol solvent of HPLC grade using accelerated solvent extractor (ASE) technique. Optimization of solvent and time was performed with 6 different solvents having different polarities to achieve maximum percentage yield of crude extract of *E coracana* (L.) for phenolic content. Reproducibility of phenolics was verified by semi-preparative HPLC-PDA. The antioxidant capacity of all phenolics was determined by rancimat study of sunflower oil using control and standard drugs such as Glipizide and Metformin. The stability period of sunflower oil was found to increase from 0.89 h to 1.04 h in the presence of 8 extracted ingredients of *E coracana* (L.), which was compared with the result of neat sunflower oil.

Emblica officinalis

Sanskrit name/Indian name: Amalaki
English name: Indian gooseberry

Antioxidant Activity of Active Tannoid Principles of *Emblica officinalis* (Amla)

Bhattacharya A, et al.

The antioxidant activity of tannoid active principles of *Emblica officinalis* (emblicanin A [37%], emblicanin B [33%], punigluconin [12%], and pedunculagin [14%]) was investigated on the basis of their effects on rat brain frontal cortical, and striatal, concentrations of the oxidative free radical scavenging enzymes, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), and lipid peroxidation, in terms of thiobarbituric acid-reactive products. These results were compared with effects induced by deprenyl, a selective monoamine oxidase B inhibitor with well documented antioxidant activity. The active tannoids of *E officinalis* (EOT) administered at doses of 5 and 10 mg/kg, and deprenyl (2 mg/kg), induced an increase in both frontal cortical, and striatal SOD, CAT, and GPX activities, with concomitant decrease in lipid peroxidation in these brain areas when administered once daily for 7 days. Acute single administration of EOT and deprenyl had insignificant effects. These results also indicate that the antioxidant activity of *E officinalis* may reside in the tannoids of the fruits of the plant, which have vitamin C-like properties, rather than vitamin C itself.
Himalaya Baby Care

Himalaya’s inception can be traced back to the year 1930 when Mr M Manal, founder of The Himalaya Drug Company, decided to present Ayurveda to the world in a contemporary form and unravel the mystery behind the 5000-year-old system of medicine. As a result, products of Himalaya are rooted in Ayurveda and backed by years of research—a true synergy of thousands of years of herbal wisdom and modern scientific research. Eight decades later, we have our presence in 67 countries with a range of over 200 products spanning pharmaceutical, personal care, baby care, and animal health. It covers the entire wellness spectrum, offering head-to-toe herbal health care catering to all kinds of people and their different needs.

Liv.52, a liver protective, and Bonnisan, a health tonic for infants and children, are classic examples of Himalaya’s innovative research. These products have become a vital part of numerous families’ health regimen. Bonnisan, for instance, is widely trusted by doctors, pediatricians, and mothers, for its safety and efficacy.

With a legacy of research expertise in herbal medicine, including therapeutic products for child health, the next step for Himalaya was “naturally” a range of herbal baby care products.

A comprehensive portfolio that suits every need of your baby, the Himalaya baby care range includes clinically proven pharmaceutical-grade herbal products based on ayurvedic formulations. Therapeutic herbs such as khus-khus, Indian madder, licorice, and olive have been used in these products to provide gentle care to your baby. Each product, clinically tested by pediatricians in leading hospitals, has 100% herbal actives specially blended to make it safe, effective, mild, and soothing.

The uniqueness of the range lies in understanding the needs of babies and combining it with Ayurveda’s philosophy of child care. Known as “Kaumara Bhritya” or complete care for the child, the philosophy encompasses nursing, nourishing, and supporting the needs of the child to grow into a happy and healthy adult.
In infantile irritant diaper dermatitis (IIDD)...

diaper rash cream Himalaya

The effective and safe therapy in diaper dermatitis

- Excellent compliance; provides relief from the very first use
- Significantly improves clinical manifestations of infantile irritant diaper dermatitis (IIDD) in 3 days, and there was complete recovery after a week’s application*
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diaper rash cream

The effective and safe therapy in diaper dermatitis
New Technologies in Knee Arthroplasty

Naziri Q, et al


Advances in surgical techniques, and implant design have increased the treatment options available to joint reconstruction surgeons. New technologies for component alignment such as custom cutting blocks and disposable cutting blocks hold the potential for more anatomic component positioning and less instrument turnover, which in turn may decrease infection rates. Improved component alignment may also be obtained with the use of computer-assisted surgery. Utilization of bone-sparing designs such as patellofemoral, unicompartmental, and bicompartmental knee arthroplasty allow the surgeon to customize treatment based on patient symptoms by addressing each compartment individually. Gender-specific designs may be useful in the setting of populations, which deviate from standard dimensions that are available in traditional unisex designs. New higher-conforming bearing designs such as rotating platform bearings allow for more natural knee kinematics, while also limiting polyethylene wear by decreasing contact stress. Newer interfaces for cementless fixation utilizing porous coated surfaces allow for biologic component fixation that has the potential to increase interface durability and implant survivorship. These new materials, designs, and techniques are challenging the traditional “gold standard” cemented total knee arthroplasty, and have the potential for developing a more durable and a prosthetic natural feeling knee. Further study is required to identify patients who are most appropriate for each new technology.

The NutriChip Project – Translating Technology into Nutritional Knowledge

Vergères G, et al


Advances in food transformation have dramatically increased the diversity of products in the market and, consequently, exposed consumers to a complex spectrum of bioactive nutrients whose potential risks and benefits have mostly not been confidently demonstrated. Therefore, tools are needed to efficiently screen products for selected physiological properties before they enter the market. NutriChip is an interdisciplinary modular project funded by the Swiss program Nano-Tera, which groups scientists from several areas of research with the aim of developing analytical strategies that will enable functional screening of foods. The project focuses on postprandial inflammatory stress that potentially contributes to the development of chronic inflammatory diseases. The first module of the NutriChip project comprised 3 in-vitro biochemical steps that mimicked the digestion process, intestinal absorption, and subsequent modulation of immune cells by the bioavailability of nutrients. The second module is a miniaturized form of the first module (gut-on-a-chip), which integrates a microfluidic-based cell co-culture system and super-resolution imaging technologies to provide a physiologically relevant fluid flow environment and allows sensitive real-time analysis of the products screened in vitro. The third module aims at validating the in vitro screening model by assessing the nutritional properties of selected food products in humans. Owing to the immunomodulatory properties of milk as well as its amenability to technological transformation, dairy products have been selected as model foods. The NutriChip project reflects the opening of food and nutrition sciences to state-of-the-art technologies, a key step in the translation of transdisciplinary knowledge into nutritional advice.
Osteoarthritis (OA), the most common form of arthritis, can lead to chronic disability, especially in elderly people. With symptoms ranging from mild to severe, OA is characterized by joint pain, tenderness, limited movement, crepitus, occasional effusion, and inflammation. It affects the joints in the hands and other weight-bearing joints, such as knees, hips, feet, and spine. In India, the prevalence rate of OA is 22% to 39%.

The disease has been described in ayurvedic texts by Sushruta in the “Vatavyadhi” chapter, under the heading “Sandhigata Vata,” while Charaka has described sandhigata vata under vatavyadhi as sandhigata anila. On the basis of symptomatology and nature of the disease, sandhigata vata is similar to OA. The authors conducted a clinical trial to assess the efficacy of Boswellia (Shallaki; Indian frankincense; *Boswellia serrata*) in the treatment of OA.

The key constituents of Boswellia are volatile oil (4%–8%), acid resin (56%–65%), and gum (20%–36%). Its active constituents are triterpenoids, which are collectively called boswellic acids. Boswellia possesses analgesic and anti-arthritic properties, which help reduce pain and inflammation without affecting the gastric mucosa. It soothes the joints and also helps regulate the levels of synovial fluid, lubricating the entire joint and making it easy to rotate and move.

Fifty-six patients aged between 40 and 70 years, with clinical signs and symptoms of OA, who attended OPD of the Department of Kayachikitsa in IPGT and RA Hospital (Gujarat Ayurved University, Jamnagar, India) were selected for the trial. Of the 56 patients 49 completed the trial. The patients were assigned to 1 of 2 groups: 29 patients in group A were treated with 500 mg Boswellia capsules, 6 g daily (in 3 divided doses) and 23 patients in group B were treated with Boswellia capsules in the same dose, duration, and frequency along with local application of Boswellia ointment. The treatment duration was 2 months.

Observations before and after treatment were graded based on subjective criteria (signs and symptoms were scored depending on their severity), radiological findings, evaluation of each patient’s mental state, and objective criteria (routine hematological and biochemical analyses, urinalysis, and estimation of C-reactive protein [CRP]).

The authors report that in patients of group A, joint pain was relieved by 73.68% and 70.96% in the left and right knee, respectively and in group B by 67.24% and 70.37% in the same joints. Both groups reported significant improvement in pain in the spine (*P* < .001) and in both shoulders (*P* < .01). Joint swelling improved by 60% and 68.42% in the left and right knee, respectively and 100% in the left ankle (*P* < .001) in group A. In group B, it improved by 87.50% and 82.14% in the left and right knee, respectively. The improvement was 100% in both shoulders (*P* < .001) in group A. Pain during movement improved in group A by 73.33% and 74.46% in the left and right knee, respectively; 100% in both hips; and 87.5% in the right ankle (*P* < .001). In group B, it improved by 71.11% and 69.50% in the left and right knee, respectively, and by 100% in the spine (*P* < .001). Stiffness improved by 69.23% and 74.19% in the left and right knee, respectively, in group A, and 74.07% and 77.78% in the left and right knee in group B (all values, *P* < .001). Crepitation of the left and right knees in group A improved by

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**Boswellia**

<table>
<thead>
<tr>
<th>Sanskrit name/Indian name:</th>
<th>Shallaki</th>
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<tr>
<td>Latin name:</td>
<td><em>Boswellia serrata</em></td>
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A 16.66% improvement was found in looseness of joints in group A ($P < .01$) and a 41.67% improvement was found in group B ($P < .001$).

Calf-muscle pain improvement ($P < .001$) and body ache and joint looseness improvement ($P < .01$ for both) were reported for group A. In group B, body ache improvement was highly significant ($P < .001$). Effects of the therapy on srotas (channels or pores) and on asthivahasrotas (the channels that bring nutrients to the bones and transport wastes) revealed improvements in both groups.

Assessment of mental status revealed that of the 56 patients, 3 (5.35%) patients had mild to moderate anxiety and 7 (12.5%) patients had mild to moderate depression. Overall, the patients in group A reported complete remission (11.54%), marked improvement (15.38%), moderate improvement (57.69%), or mild improvement (11.54%); in group B, none of the patients reported complete remission, 8.69% showed marked improvement, 69.56% reported moderate improvement, and 21.74% showed mild improvement. Overall assessment suggests that improvement was better in group A, write the authors, further explaining that the majority of those patients were younger and had milder symptoms.

Radiological findings included statistically significant improvements in joint space, subarticular sclerosis, and synovial effusion of 66.67%, 57.14%, and 87.50%, respectively ($P < .001$) in group A, while in group B, only joint space and synovial effusion were improved (by 46.67% and 100%, respectively; $P < .001$).

CRP and serum triglycerides were reduced significantly by 68.41% and 34.35%, respectively, in group A ($P < .001$). In group B, serum triglycerides decreased by 23.90% ($P < .001$), but CRP increased ($P > .05$). The reduction in serum triglycerides in both groups confirms the hypolipidemic effects of Boswellia.

The authors conclude that after a course of therapy for 2 months, symptomatic improvement was observed in both the groups at various levels with promising results in the patients of group A. A randomized, placebo-controlled, clinical trial is needed to verify the findings of this trial.

— Henson S. HerbalGram. 2012.
What is teeth sensitivity?

If you experience a tingling pain or sudden flash of pain after eating...

- Sweet
- Cold
- Hot
- Sour foods

What causes teeth sensitivity?

- Brushing your teeth too hard
  Aggressive brushing habits can cause the gums to sag down

- Poor oral hygiene
  It leads to accumulation of plaque and increases the gap between teeth & gums

- Frequently eating acidic foods or drinking acidic beverages
  It is not advisable to brush immediately after consuming acidic foods/beverages, as these foods make the enamel soft

- Untreated cavities
  If left untreated, it may lead to other dental problems

Sensitive teeth requires your immediate attention!

How does teeth sensitivity occur?

Teeth sensitivity occurs when the dentin (middle layer) of a tooth is exposed due to receding gums (gums sag down).
How to manage sensitive teeth?

**Use a soft-bristled toothbrush**
- Brush gently and carefully around the gum line

**Maintain good oral hygiene**
- Brush your teeth gently twice a day by using HiOra-K toothpaste, specifically formulated to address the problem of sensitive teeth
- Rinse your mouth with HiOra-K mouthwash twice daily to reach the interdental areas and helps in faster relief

**Watch what you eat**
- Avoid excessive consumption of acidic (sour) foods (like pickles, sauces, tamarinds, and lemons), carbonated drinks, and sweets

**Regular visit to Dentist**
- Visit your dentist once in every 3 months

How does HiOra-K toothpaste benefit people with sensitive teeth?

1. **Effectively reduces teeth sensitivity**
   Blocks pain signals from teeth

2. **Occludes exposed dentinal tubules**
   Plug the open holes on the dentin

3. **Strengthens the gums**
   Reduces the gap between teeth & gums

Sensitive teeth requires your immediate attention!

The synergistic combination of HiOra-K + HiOra-K provides rapid relief from teeth sensitivity.

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– Editor
Upcoming Events

**Event:** Women’s Health  
**Date:** March 2 to 9, 2013  
**Venue:** California, USA  
For more details, log on to http://www.continuingeducation.net/coursedetails.php?program_number=1181

**Event:** Endocrinology and Rheumatology: The Most Useful Topics from Two Specialties  
**Date:** March 4 to 8, 2013  
**Venue:** Florida, USA  
For more details, log on to http://www.ams4cme.com/www/LiveSeminars/SEMLA-2720130304.aspx

**Event:** The 11th International Conference on Alzheimer’s and Parkinson’s Disease  
**Date:** March 6 to 10, 2013  
**Venue:** Florence, Italy  
For more details, log on to http://www2.kenes.com/adpd/pages/home.aspx

**Event:** Infectious Diseases: Adult Issues in the Outpatient and Inpatient Settings  
**Date:** March 11 to 15, 2013  
**Venue:** Florida, USA  
For more details, log on to http://www.ams4cme.com/www/LiveSeminars/SEMLA-2720130311.aspx

**Event:** Imaging in Cancer Drug Development  
**Date:** March 13 to 14, 2013  
**Venue:** London, United Kingdom  
For more details, log on to http://www.smi-online.co.uk/goto/cancer-imaging7.asp

**Event:** Principles of Critical Care Medicine for Non-Intensive Care Specialists  
**Date:** March 14 to 16, 2013  
**Venue:** Massachusetts, USA  
For more details, log on to http://www.criticalmedboston.com

**Event:** Neurology  
**Date:** April 6 to 13, 2013  
**Venue:** Florida, USA  
For more details, log on to http://www.continuingeducation.net/coursedescription.php?topic=Neurology_CME_Caribbean_Cruise_April_2013_Oasis

**Event:** 1st International Workshop on Clinical Pharmacology of Antifungal Drugs & Fungal Diseases  
**Date:** April 26, 2013  
**Venue:** Berlin, Germany  
For more details, log on to http://www.eme-medicaleducation.com/

**Event:** 7th Conference on Experimental and Translational Oncology  
**Date:** April 20 to 24, 2013

**Event:** BIOMED 2013  
**Date:** April 24 to 26, 2013  
**Venue:** Budapest, Hungary  
For more details, log on to http://www.wessex.ac.uk/13-conferences/biomed-2013.html

**Event:** The 1st Seoul International Congress of Endocrinology & Metabolism  
**Date:** May 2 to 5, 2013  
**Venue:** Seoul, Korea  
For more details, log on to http://www.seoul-endo.org/index.html

**Event:** 1st Global Conference: The Boundaries of Reproduction  
**Date:** May 12 to 14, 2013  
**Venue:** Prague, Czech Republic  
For more details, log on to http://www.inter-disciplinary.net/probing-the-boundaries/persons/the-boundaries-of-reproduction/call-for-presentations/
Introduction
HiOwna, a multi-ingredient nutritional health drink supplement, is designed to provide overall nutritional benefits to adults and elderly. HiOwna comprises of pea protein, soy protein isolate, skimmed milk powder and is fortified with well-known herbs, vitamins and minerals that provide nourishment and promote general health and well-being.

HiOwna is a health supplement and must be taken along with regular daily diet.

Composition
Each 25 g of HiOwna (vanilla flavor) contains:

<table>
<thead>
<tr>
<th>Pdrs.</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarkara</td>
<td>10.50</td>
</tr>
<tr>
<td>Kshira**</td>
<td>4.55</td>
</tr>
<tr>
<td>Kalaya (Pisum sativum)</td>
<td>2.00</td>
</tr>
<tr>
<td>Kharjura (Phoenix dactylifera)</td>
<td>0.83</td>
</tr>
<tr>
<td>Amalaki (Emblica officinalis)</td>
<td>0.375</td>
</tr>
<tr>
<td>Maricha (Piper nigrum)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Each 25 g of HiOwna (chocolate flavor) contains:

<table>
<thead>
<tr>
<th>Pdrs.</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarkara (Saccharum officinarum)*</td>
<td>10.70</td>
</tr>
<tr>
<td>Kshira**</td>
<td>4.55</td>
</tr>
<tr>
<td>Kalaya (Pisum sativum)</td>
<td>2.00</td>
</tr>
<tr>
<td>Kharjura (Phoenix dactylifera)</td>
<td>0.83</td>
</tr>
<tr>
<td>Amalaki (Emblica officinalis)</td>
<td>0.375</td>
</tr>
<tr>
<td>Maricha (Piper nigrum)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

*Used in the form of sucrose.
**Used in the form of skimmed milk powder.

Other ingredients: Vitamins and Minerals.

Vitamins: A, C, D, E, K, and B-complex [B1 (thiamine), B2 (riboflavin), niacinamide (B3), pantothenic acid (B5), B6 (pyridoxine), biotin (B7 or H), and folic acid (B9), and B12 (cobalamin)].

Minerals: Calcium, phosphorus, iron, magnesium, zinc, chromium, selenium, and molybdenum. Base q.s.†

†Maltodextrin, isolated soy protein, cocoa powder#, and nature-identical flavoring substance.

#Present only in HiOwna chocolate variant.

Health Benefits
HiOwna is a balanced health drink supplement that contributes to overall health through its nutritive and health-promoting, immunomodulatory, nutrient absorption-enhancing, gastroprotective, antistress, adaptogenic, and antioxidant actions.

HiOwna contains various essential macronutrients and micronutrients. The macronutrients (proteins, carbohydrates, and fats) provide energy, promote growth and development, and regulate body functions. The micronutrients (vitamins and minerals) meet the additional nutritional demands at various physiological stages.

HiOwna revives physical capacity, raises the threshold of fatigue, and promotes well-being. HiOwna facilitates respiratory functions, regulates fat and carbohydrate metabolism, improves appetite, digestion and assimilation. The antistress and adaptogenic actions of HiOwna retard degenerative changes and accelerate cellular regeneration and repair.

On the whole, HiOwna rejuvenates the entire body.

Indications
As a daily nutritional health drink supplement in adults and elderly, and also in:

- Postoperative convalescence
- Prolonged illness
- Occupational stress
Dosage
4 heaped tablespoons (approximately 25 g) twice daily.

Serving instructions:
Advise to: Add 4 heaped tablespoons (approx. 25 g) of HiOwna to a cup of lukewarm/cold milk or water, stir briskly until mixed well, and add sugar to taste, if required.

Health Benefits of Principal Ingredients
Nutritive and health-promoting actions
Studies have demonstrated the hemopoietic activity of *P. dactylifera* fruit extracts. It was reported that *P. dactylifera* may possess properties capable of supporting increased erythropoietin synthesis by the liver, which in turn stimulates the bone marrow to produce more blood cells.

*P. dactylifera* fruits have also been proven to have nutritional importance. They are a good source of iron and potassium, a fair source of calcium, chlorine, copper, magnesium and sulphur, and a minor source of phosphorus. In addition, they are a source of 16 amino acids and vitamins A, B1, and B2.

*P. dactylifera* fruits are used to improve physical strength.

*P. sativum* is of great nutritional importance due to its high content of protein (aspartic acid, tyrosine, and serine), complex carbohydrates, dietary fiber, minerals (calcium, potassium, phosphorus, and iron), vitamins (carotene, thiamine, riboflavin, niacinamide, and vitamin C), and antioxidant compounds.

*S officinarum* has high sucrose content. Reports have suggested that sucrose supplementation increases energy intake.

Kshira (milk) is widely used from ancient era as a food and a base of medicament. It attains high nutritive value because of its components like proteins, lipids, vitamins, enzymes, and minerals, which contribute to overall health and well-being.

Skimmed milk powder is rich in casein. Casein exists in skimmed milk as a complex of calcium caseinate and calcium phosphate, which are readily absorbable forms of calcium. Skimmed milk powder, by virtue of its thickening and water-binding properties, binds well with herbal actives and minerals.

Micronutrients such as vitamins and minerals, when given as supplements or fortified foods, were found to have a positive effect on cognitive performance.

1. Immunomodulatory action:
Milk has a dual role of nutrition and immunological protection.

*E officinalis* is shown to be an effective immunostimulant by way of significantly increasing DTH (Delayed Type of Hypersensitivity) activity, MMI (Macrophage Migration Index), and NBT (Nitroblue Tetrazolium Test) dye reduction of macrophages. Thus, *E officinalis* stimulates humoral as well as cell-mediated immunity. This prevents repeated infections.

2. Gastroprotective and nutrient absorption-enhancing actions:

*E officinalis* exhibits significant antiulcer and cytoprotective properties. Tannins, with their protein-precipitating and vasoconstricting effects could prove beneficial in preventing ulcer development, thus exhibiting gastroprotective activity.

*P. nigrum* stimulates the taste buds that signal and alert the stomach, thereby normalizing gastric secretions, and is hence used to relieve digestive disorders.

*P. nigrum* offers protection in a dose-dependent manner against the damage caused by necrotizing agents to gastric mucosa, thus exhibiting significant gastroprotective activity.

It has been reported that piperine (active principle of *P nigrum*), by favorably stimulating the digestive enzymes of pancreas, enhances the digestive capacity and normalizes the gastrointestinal food transit time, thus enhancing the absorption and bioavailability of herbal actives and nutrients.

3. Antistress and adaptogenic actions:

*E officinalis* has significant antistress and adaptogenic activities against a number of behavioral, biochemical, and physiological perturbations induced by unpredictable stress.

*E officinalis* is also reported to have significantly ameliorated the oxidative stress induced by scopolamine in experimental models.

4. Antioxidant action:
Recent studies indicate that fruit extracts of *P. dactylifera* have potent antioxidant activity, which is attributed to the wide range of phenolic compounds including p-coumaric acid, ferulic acid, sinapic acid, flavonoids, and procyanidins. Growing evidence indicates that diets rich in fruits and vegetables provide protection against chronic diseases such as cardiovascular disease. *P. dactylifera* fruits are a significant source of daily dietary antioxidants.

*S officinarum* consists of phenolic compounds that exhibit antioxidant action.

*P. dactylifera* may have the potential as a protective agent against cellular damage, a cause of oxidative stress.
*E. officinalis* has antioxidant activity, which is attributed to the polyphenols including flavonoids and sterols with significant free radical-scavenging property. *E. officinalis* extract reduces the COX-2 and iNOS expression levels by inhibiting NF-κB activation. *E. officinalis* has been reported to be a very useful antioxidant in the prevention of age-related renal disease. *E. officinalis* extract contains tannoid principles, namely emblicanin A, emblicanin B, punigluconin and pedunculagin, reported to possess antioxidant activity in vitro and in vivo.
Introduction

Bresol is a phytopharmaceutical formulation recommended for allergic respiratory disorders, and provides symptomatic relief in allergic bronchitis and allergic rhinitis.

Composition

Each 5 ml of Bresol syrup contains:

Exts.

Haridra (*Curcuma longa*) 100.5 mg
Tulasi (*Ocimum sanctum*) 50 mg
Vasaka (*Adhatoda vasica*) 50 mg
Trikatu 8 mg
Triphala 8 mg
Vidanga (*Embelia ribes*) 8 mg
Musta (*Cyperus rotundus*) 8 mg
Tvak (*Cinnamomum zeylanicum*) 5 mg
Ela (*Elettaria cardamomum*) 5 mg
Patra (*Cinnamomum tamala*) 5 mg
Nagakesara (*Mesua ferrea*) 5 mg

Each Bresol tablet contains:

Exts.

Haridra (*Curcuma longa*) 100.5 mg
Tulasi (*Ocimum sanctum*) 50 mg
Vasaka (*Adhatoda vasica*) 50 mg
Trikatu 8 mg
Triphala 8 mg
Vidanga (*Embelia ribes*) 8 mg
Musta (*Cyperus rotundus*) 8 mg
Tvak (*Cinnamomum zeylanicum*) 5 mg
Ela (*Elettaria cardamomum*) 5 mg
Patra (*Cinnamomum tamala*) 5 mg
Nagakesara (*Mesua ferrea*) 5 mg

Clinical Pharmacology

Bresol has antihistaminic, mast cell-stabilizing, interleukin (IL)-downregulating, bronchodilatory, antitussive, mucolytic, antimicrobial, anti-inflammatory and antioxidant actions, which synergistically act to provide symptomatic relief in allergic respiratory conditions.

Bresol’s antihistaminic property helps control symptoms associated with respiratory disorders. The mucolytic and bronchodilatory properties of Bresol help liquefy the sputum and ease expectoration, thus relieving nasal and bronchial congestion. Bresol’s antimicrobial action combats the infections caused by Gram-positive and Gram-negative bacteria.

Indications

- Allergic rhinitis
- Allergic bronchitis
- Bronchial asthma
- Pollen allergy

Dosage

Syrup:
Children (above 6 months): 1 to 2 teaspoonfuls two or three times daily.
Adults: 2 teaspoonfuls two or three times daily.

Tablet:
Children: 1 tablet two or three times daily.
Adults: 2 tablets two or three times daily.

Adverse Effects

No adverse effects have been reported.

Contraindications

No absolute contraindications.

Special Precautions

None.

Drug Interactions

No clinically significant drug interactions have been reported.

Presentation

Syrup: Pilfer-proof bottles of 100 mL.
Tablet: Sealed packs of 60 tablets.
Pharmacological Actions of Principal Ingredients

1. Antihistaminic, mast cell-stabilizing, and interleukin-downregulating actions:

   *O sanctum* has been demonstrated to protect against histamine- and pollen-induced bronchospasm, and inhibit antigen-induced histamine release from sensitized mast cells. Eugenol, extracted from the essential oil of *O sanctum*, possesses a membrane-stabilizing effect on synaptosomes, erythrocytes and mast cells, which accounts for the therapeutic potential of *O sanctum* in the management of inflammatory and allergic disorders. *O sanctum* is used in catarrh and bronchitis, possibly due to its varied pharmacological activities.

   Basophils, mast cells, and their preformed de novo synthesized mediators play a pivotal role in the pathogenesis of allergic disorders. Experimental studies show that IL-4 level in bronchoalveolar lavage fluid (BALF) was increased in sensitized rats when they were exposed to antigen/allergen, and this upregulation of IL-4 was reversed by treatment with HK-07 (Bresol). The effect may be due to inhibition of Th2 cell formation or function. It is important to note that IL-4 is one of the important triggering factors for release of IgE (reaginic) antibodies, which are responsible for allergy. IL-4 is involved in allergen-induced eosinophilic inflammation and bronchial hyperresponsiveness.

   Curcumin, isolated from *C longa*, inhibits protease-activated receptor PAR2- and PAR4-mediated human mast cell activation.

2. Bronchodilatory action:

   Alkaloids of *A vasica* enhance the bronchodilatory action, and have potential value in the treatment of inflammatory lung diseases like bronchial asthma. They show a noted protection against allergen-induced bronchial obstruction, thus showing their protective role in airway maintenance. *M ferrea* is found to potentiate the bronchodilatory activity of isoprenaline, both in vitro and in vivo.

3. Antitussive action:

   *O sanctum* exerts antitussive effect by central action, probably mediated by both opioid and GABAergic systems, which soothes the cough associated with various reversible airway disorders including those of allergic origin. The antitussive activity of *A vasica* is comparable with that of codeine.

4. Mucolytic action:

   Benzylamines, bromhexine and ambroxol, the semi-synthetic derivatives of vasicine from *A vasica*, are widely used as mucolytics that may be helpful in relieving the viscous sputum associated with various coughs.

5. Antimicrobial action:

   *O sanctum* and *C rotundus* have strong anti-inflammatory actions that control the inflammation associated with inflammatory respiratory conditions.

6. Anti-inflammatory action:

   *O sanctum* and *C rotundus* have strong anti-inflammatory actions that control the inflammation associated with inflammatory respiratory conditions.

7. Antioxidant action:

   Oxidative stress has an important role to play in the etiopathology of allergic respiratory tract diseases.

8. Other activities:

   Piperine present in *P nigrum* and *P longum* (ingredients of Trikatu) has shown to be a bioavailability enhancer, either by promoting rapid absorption from the GI tract, or by protecting the drug from being metabolized/oxidized in its first passage through the liver after being absorbed, or by a combination of both the mechanisms.
Evaluation of Efficacy and Safety of Liv.52® Tablet in Acute Alcoholic Hepatitis: An Open Clinical Study

Dange SV


**Abstract**

This study was conducted to evaluate the clinical efficacy and safety of Liv.52 tablet in acute alcoholic hepatitis. Thirty-four male patients with a mean age of 45.88 ± 9.52 years were enrolled for the open clinical trial. All the patients received Liv.52 tablet in recommended doses for a period of 4 months. Patients were examined and scored for symptoms such as jaundice, anorexia, nausea/vomiting, fever, and pruritus at initiation and thereafter at monthly intervals for 4 months. Treatment with Liv.52 tablet showed significant improvement in clinical signs and symptoms as well as biochemical parameters. Though there was a difference in hematological parameters before and after treatment with Liv.52 tablet the values were within the normal range, which clearly indicates the safety of the drug.

**Key Words**

Liv.52 tablet, alcoholic hepatitis, open clinical study

**Introduction**

Sustained excessive alcohol consumption is a brain-centred addictive behavioral disorder that crosses all boundaries of gender, race, age, economic strata and in many patients might lead to alcoholic liver disease (ALD). It may well represent the oldest form of liver injury known to humankind. Evidence suggests that fermented beverages existed as early as the Neolithic period (circa 10,000 BC). Alcohol consumption across the world varies in terms of geography; approximately two-thirds of adult Americans consume alcohol. Patterns of alcohol intake also vary; a majority drink small or moderate amounts and do so without evidence of clinical disease, while a subgroup of drinkers, drinks excessively, develops physical tolerance and withdrawal, and is diagnosed with alcohol dependence.

Heavy drinking significantly increases morbidity and mortality from infectious diseases and the risk of cardiovascular, brain, pancreatic, renal, cerebral, and oncological diseases. ALD represents a spectrum of clinical illness and morphological changes that range from fatty...
 Liver to hepatic inflammation and necrosis (alcoholic hepatitis [AH]) to progressive fibrosis (alcoholic cirrhosis). Furthermore, sustained excessive alcohol intake favors the progression of other liver diseases, such as chronic viral hepatitis and also increases the risk of hepatocellular carcinoma.

ALD is initiated by different cell types in the liver and a number of different factors including products derived from alcohol-induced inflammation, ethanol metabolites, and indirect reactions from those metabolites, as well as genetic predisposition. Ethanol oxidation results in the production of metabolites that have been shown to bind and form protein adducts, and increase inflammatory, fibrotic, and cirrhotic responses. Increase in inflammatory cytokine release is greatly influenced by the lipopolysaccharide (LPS), which has many deleterious effects and plays a significant role in a number of disease processes. In ALD, LPS is thought to be derived from a breakdown in processes. In ALD, LPS is thought to be derived from a breakdown in processes. In ALD, LPS is thought to be derived from a breakdown in processes.

Increase in inflammatory cytokine release is greatly influenced by the lipopolysaccharide (LPS), which has many deleterious effects and plays a significant role in a number of disease processes. In ALD, LPS is thought to be derived from a breakdown in the intestinal wall enabling LPS from resident gut bacterial cell walls to leak into the blood stream.8

The diagnosis of ALD is based on a combination of features, including a history of significant alcohol intake, clinical evidence of liver disease, and supporting laboratory abnormalities.9

Diagnosing AH can be challenging as the disease not only has widely varying presentations but can also mimic a bacterial infection and/or biliary obstruction in severe cases. A detailed and thorough history remains the cornerstone of diagnosis10 and obtaining such a history can be rather difficult if patients feel ashamed about disclosing their drinking habits. Physical findings include hepatomegaly, ascites, encephalopathy (ranging from asterixis only to coma) and gastrointestinal bleeding requiring transfusion, especially if the cause is esophageal varices. Nonspecific findings of jaundice and malnutrition are also commonly seen.10-12

Jaundice is present in essentially 100% of patients with severe AH. Notably, body temperature ranging from 100.4ºC to 104ºC, due to AH and not attributable to infection can be seen in over half of patients diagnosed with severe AH.11

A number of laboratory abnormalities, including elevated serum amino-transferases have been reported in patients with alcoholic liver injury and are used to diagnose ALD. In severe AH serum AST is typically elevated to a level 2 to 6 times its normal upper limits.13

Proper diagnosis and management of the complications of ALD are vital to alleviating the symptoms of illness, improving quality of life, and possibly decreasing mortality. The complications of ALD reviewed here are ascites (accumulations of fluid in the abdominal cavity), infections in this fluid that develop without any apparent cause (ie, spontaneous bacterial peritonitis [SBP]), hepatorenal syndrome, and esophageal varices.

Treatment strategies for ALD include lifestyle changes to reduce alcohol consumption, cigarette smoking, and obesity; nutrition therapy; pharmacological therapy; and possibly liver transplantation. Abstinence from alcohol is vital to prevent further liver injury, scarring, and liver carcinoma; and benefits patients at every stage of the disease. Malnutrition is prevalent in AH and cirrhosis, especially in end-stage ALD and can range from deficiency in individual nutrients (eg, zinc, folate) to global protein—calorie malnutrition. Several pharmacological agents like Propylthiouracil14 Colchicine,15 Pentoxifylline16 are found to be beneficial in AH. Corticosteroids are the most extensively studied form of therapy for AH, but their role remains limited. The rationale for steroid use is to decrease the immune response and the proinflammatory cytokine response.17

Aim

To evaluate the safety and clinical efficacy of Liv.52 tablet, a polyherbal hepatospecific formulation, in patients suffering from AH

Materials and Methods

This was an open, prospective clinical trial undertaken on 34 male patients in the age group of 18 to 60 years presenting with acute AH at the Department of Medicine, DY Patil Medical College (Pune, India) between April 2010 and September 2011, after getting an approval from the Institutional Ethical Committee. All the participants were informed about the voluntary nature of the trial and written consents were obtained. The study was done in accordance with regulatory standards of good clinical practice (GCP).

Study procedure

Thirty-four male patients in the age group of 18 to 60 years presenting with acute AH and having jaundice, anorexia, nausea, vomiting, fever, and pruritus as the predominant symptoms were enrolled for the trial after obtaining the written informed consent form. Detailed history of the duration, frequency, and severity of the symptoms, and details suggestive of significant alcohol intake were elicited. All patients underwent thorough physical examination and vital tests and results were recorded in case report forms (CRFs). Laboratory investigations were performed for complete blood count, SGPT, serum bilirubin, total protein, albumin, and globulin. All the patients received 2 tablets of Liv.52 twice daily for a period of 4 months. Safety and
efficacy of the investigational product was evaluated at monthly intervals up to 4 months. Clinical and laboratory evaluations were repeated at the end of 4 months.

Inclusion criteria
Male patients in the age group of 18 to 60 years presenting with acute AH and having jaundice, anorexia, nausea, vomiting, fever, and pruritus as the predominant symptoms and who were willing to give the informed consent and comply with the study procedures were included for the study.

Follow-up and assessment
All the subjects were followed-up at monthly intervals up to 4 months and at each visit patients were evaluated for reduction in signs and symptoms and also their overall responses to the treatment were evaluated. Clinical symptoms such as jaundice, anorexia, nausea/vomiting, fever and pruritus were scored at-entry and at every follow-up visit using 0 to 4 point scale as none, mild, moderate or severe based on the severity of symptoms.

Primary and secondary endpoints
The predefined primary endpoint was reduction in the signs and symptoms of acute AH after treatment with the study drug. The predefined secondary endpoints for safety were assessed by incidence of adverse events and compliance to the drug therapy.

Adverse events
All of the study participants completed the study and none of them reported any adverse effects.

Statistical Analysis
Repeated measures of ANOVA with Friedman’s test followed by Dunnett’s multiple comparison test or Student’s paired t-test were used for statistical analysis. The results were expressed as mean ± SD. The minimum level of significance was fixed at P < .05. Statistical analysis was performed using Graphpad Prism version 4.03 for Windows (Graphpad software, San Diego, CA, USA).

Results
An open clinical trial was conducted with Liv.52 tablet in 34 male patients with a mean age of 45.88 ± 9.52 years. The mean body weight of the participants at the initiation of the study was 61.94 ± 11.50 and the mean height was 162.03 ± 5.77. All the patients received Liv.52 tablet in recommended doses for a period of 4 months.

Clinical evaluations for jaundice, anorexia, nausea/vomiting, fever, and pruritus were scored at initiation and monthly thereafter for 4 months using a 0 to 4 point scale as none, mild, moderate, and severe based on the severity of symptoms. Clinical parameters of pulse (80.15 ± 4.43), BP (134.35 ± 14368/83.76 ± 9.83), CVS (sounds/murmurs), RS, GIT, and CNS (general) were found to be normal in all the patients. Hemoglobin, WBC count, and differential counts were performed as part of routine hematology and biochemical observations included SGPT, serum bilirubin, total protein, albumin and globulin. The results were expressed as mean ± SD for hematological and clinical evaluations.

No adverse drug reactions were reported following treatment with Liv.52 tablet for a period of 120 days. Only 1 case of drop-out was recorded during the trial period, thus indicating excellent patient compliance. Treatment with Liv.52 tablet showed significant improvement in clinical signs and symptoms as well as biochemical parameters. Though there was a difference in hematological parameters observed before and after treatment with Liv.52 tablet the values were within the normal range, which clearly indicates the safety of the drug. The study outcome as reported by the investigator showed marked improvement in 7.41%, moderate improvement in 33.33%, slight improvement in 33.33, and no change in 25.92% of the cases. The overall impression as reported by the patients themselves showed complete recovery in 3.7%, marked improvement in 11.11%, moderate improvement in 7.41%, slight improvement in 55.56% and no change in 22.22% of the cases.

Significant relief from clinical symptoms was observed from 2nd month of treatment onwards until the end of the study (Table 1). Significant improvements in hematology and liver function parameters were also observed (Tables 2 and 3).

There were no clinically significant adverse reactions either reported or observed during the entire study period; and overall compliance to the treatment was adequate.

Discussion
ALD encompasses a spectrum of injuries ranging from simple steatosis to frank cirrhosis. It may well represent the oldest form of liver injury known to humankind. Alcohol remains a major cause of liver disease worldwide. It is common for patients with ALD to share risk factors for simultaneous injury from other liver insults (eg, coexisting non-alcoholic fatty liver disease or chronic viral hepatitis).

Liv.52 tablet is a hepato-specific formulation, designed for the management of liver disorders. It has a wide spectrum of therapeutic applications. It restores the metabolic efficiency of the liver in various etiological forms of hepatocellular jaundice like infective and chronic active hepatitis, drug-induced jaundice like infective and chronic active hepatitis, drug-induced
hepatitis, and alcohol-induced hepatic damage. Some of the potent herbs in Liv.52 tablets are *Capparis spinosa*, *Cichorium intybus*, mandura bhasma, *Solanum nigrum*, *Terminalia arjuna*, *Cassia occidentalis*, *Achillea millefolium* and *Tamarix gallica*. These herbs possess significant hepatoprotective activity and have been used for centuries in the ayurvedic approach to healthcare. These herbs have been used by thousands of people over many years and their benefits are well documented. They are widely available in public domain, which confirms the safety and efficacy of herbal formulations.

p-Methoxy benzoic acid from *C. spinosa* has potent hepatoprotective activity against chemically-induced hepatotoxicity, prevents elevation of malondialdehyde levels (plasma and hepatic) and enzyme levels (AST and ALT).18-20 It improves the functional efficiency of the liver and spleen with protective action on the histological architecture of the liver and a salutary effect on liver glycogen and serum proteins.21 Flavonoids of *C spinosa* have significant antioxidant activity as demonstrated by lipid peroxidation, bleaching of free radicals, and auto-oxidation of iron ions.22

*C intybus* protects the liver against alcohol toxicity. It increases circulating leukocytes, splenic plaque-forming cells, hemagglutination titers, secondary IgG antibody response, phagocytic activity, natural killer cell activity, cell proliferation, and IFN-γ secretion.23,24 Its hepatoprotective activity suppresses the oxidative degradation of DNA in tissue debris.25 It also has potent antioxidant action as evident by its free radical scavenging effects, inhibition of hydrogen peroxide and iron chelation.26,27

*S nigrum* protects DNA against oxidative damage,28 and also acts as a potent scavenger of hydroxyl and diphenyl picryl hydrazyl radicals.29

### Table 1. Effect of Liv.52 Tablet on Clinical Signs and Symptoms in Patients with AH (n = 50)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment Duration</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 30</td>
</tr>
<tr>
<td>Jaundice</td>
<td>2.21 ± 0.74</td>
<td>1.79 ± 0.86</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2.46 ± 0.71</td>
<td>1.64 ± 0.96</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2.48 ± 0.57</td>
<td>1.54 ± 0.83</td>
</tr>
<tr>
<td>Fever</td>
<td>0.47 ± 0.66</td>
<td>0.24 ± 0.60</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.85 ± 1.00</td>
<td>0.58 ± 0.79</td>
</tr>
</tbody>
</table>

Statistical significance: a*P values as compared with day 0; b*P values as compared with day 30; and c*P values as compared with day 90.

### Table 2. Effect of Liv.52 Tablet on Hematological Parameters in Patients with AH

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment Duration</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 120</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.72 ± 1.71</td>
<td>12.11 ± 1.56</td>
</tr>
<tr>
<td>WBC (cells/ mm³)</td>
<td>10,030 ± 2181</td>
<td>9033 ± 1504</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>75.24 ± 5.30</td>
<td>70.59 ± 2.16</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>20.31 ± 5.08</td>
<td>23.17 ± 4.21</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>2.07 ± 1.96</td>
<td>2.36 ± 2.30</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>2.45 ± 1.35</td>
<td>4.31 ± 1.34</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
</tr>
</tbody>
</table>

NS, not significant. Significance as compared with respective day 0 values.

### Table 3. Effect of Liv.52 Tablet on Biochemical Parameters in Patients with AH

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment Duration</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 120</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>72.34 ± 12.60</td>
<td>35.83 ± 7.92</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>2.64 ± 0.93</td>
<td>1.19 ± 0.44</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>5.93 ± 0.66</td>
<td>6.33 ± 0.75</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.87 ± 0.66</td>
<td>3.09 ± 0.71</td>
</tr>
<tr>
<td>Globulin (g/dL)</td>
<td>3.06 ± 0.54</td>
<td>3.17 ± 0.57</td>
</tr>
</tbody>
</table>

Significance as compared with respective day 0 values.
The cytoprotective effect of *S nigrum* against gentamicin-induced toxicity showed a significant inhibition of cytotoxicity and hydroxyl radical scavenging potential.30

*T arjuna* reduces cholesterol levels and is also useful in liver disorders.31,32 It has potent antioxidant activity, hepatoprotection.38 hepatic enzymes, thus providing peritoneal macrophages.34 It inhibits synthase levels in LPS-stimulated production, and terminoside A decreases inductible nitric oxide synthase levels in LPS-stimulated peritoneal macrophages.34 It inhibits viral attachment and penetration,35 thus possesses antiviral activity. It also has supportive antibacterial activity.36

*C occidentalis* has significant hepatoprotective effects in chemically-induced liver damage.37 It modulates hepatoprotective activity.38

*A millefolium* is beneficial in chronic hepatitis39 and has anti-hepatoma activity.40

*T gallica* is a hepatic stimulant, and safe in patients suffering from AH. Significant relief was observed. Therefore, it may be concluded that Liv.52 tablet is effective and safe in patients suffering from AH.

**Conclusion**

Results of the present clinical trial showed that Liv.52 tablet significantly relieved symptoms in patients suffering from AH. Significant relief from the clinical symptoms was noted from 2nd month of treatment onwards until the end of the study. A significant improvement in liver function parameters was also observed. There were no adverse reactions either reported or observed during the entire study period and overall compliance to the treatment was adequate. Therefore, it may be concluded that Liv.52 tablet is effective and safe in patients suffering from AH.

**References**

I am prescribing Liv.52 since 10 years. It has been my drug-of-choice for treating hepatic disorders. I find Liv.52 very effective in the treatment of jaundice and anorexia. I would like to thank The Himalaya Drug Company for providing documented and well-researched products.

**Dr Satish Tomar**, Brahmpuri, New Delhi

I found Liv.52 to be very useful, effective, and safe in the treatment of liver disorders. I have been prescribing Liv.52 for the last two decades in conditions such as viral hepatitis, drug-induced hepatitis, and fatty liver. I also prescribe Liv.52 in patients who are on anti-tubercular drugs. It has provided excellent results.

**Dr KK Sharma**, Etawah, Uttar Pradesh

Liv.52 is an excellent liver-protector, appetizer, and a general tonic. I treated a patient who was suffering from hepatitis B for 6 months with Liv.52 and got good results within 30 hours. Liv.52 gives excellent results even in acute diseases.

**Dr BH Aghera**, Junagadh, Gujarat

Liv.52 is a beneficial drug, and there is no comparison to it. I have diagnosed and treated a challenging case of child malnutrition with splenomegaly with Liv.52. Hats off to Liv.52!

**Dr MS Dhruvakumar**, Lingarajapuram, Bangalore

Since 1965, I have been prescribing Liv.52 tablet and syrup for problems of acute and chronic liver disease, acute and chronic constipation, anorexia, and as a supportive therapy for alcoholics who wanted to give-up alcohol. In 1988, a patient suffering from viral hepatitis recovered after 3 weeks of treatment with Liv.52 tablet.

**Dr NN Asokan**, Muvattupuzha, Kerala

I have been prescribing Liv.52 with anti-tubercular drugs. It is a hepatoprotective- and hepatoregenerative-drug; useful in improving appetite. In one of the cases of severe hepatitis showing increase in liver enzymes (alanine transaminase and aspartate aminotransferase), there was a significant improvement with Liv.52 and the patient was clinically better.

**Dr Vijay Khurana**, Agra, Uttar Pradesh

I have found Liv.52 to be a wonder drug in my clinical cases, especially as a hepatoprotective and appetite-stimulant in chronic debilitating diseases and geriatric patients. I came across 1 challenging case of polytrauma with multiple fractures of lower limbs, operated with plates. He developed liver dysfunction due to hepatitis postoperatively, which I successfully treated with Liv.52.

**Dr Suresh Dargan**, Dwarka, New Delhi

Liv.52 is a wonderful drug from Himalaya. It has been showing good results consistently for years now. It is one of the “marvels of medicine.” I prescribed Liv.52 tablets to a patient who was on alcoholic drinks for a long time. He took the medication non-stop for 1 year. His liver improved remarkably, both in terms of function and size. He was prevented from developing cirrhosis.

**Dr Hemant Bhatt**, Mumbai, Maharashtra

Liv.52 gives excellent results to my patients. I treated a patient having alanine transaminase levels up to 187. After starting Liv.52, it reduced to 97 and the patient was cured. I am also prescribing Liv.52 to HIV positive patients, and getting good results.

**Dr Govindabhai Patel**, Mehsana, Gujarat

Since the last 2 decades, I have been prescribing Liv.52 widely for acute hepatitis and chronic liver disease including alcoholic liver disease, anorexia of unknown origin, and hyperemesis. I have successfully treated with Liv.52, a challenging case of unresolved hepatitis with high bilirubin levels.

**Dr Purushotam**, Hubli, Karnataka

I have been prescribing Liv.52 DS to diabetic patients having loss of appetite and jaundice; to TB patients; and both cases have shown extremely good results. The product has shown good results both clinically and pathologically - like normalization of serum bilirubin, alanine transaminase, aspartate aminotransferase, and alkaline phosphatase levels.

**Dr PR Kumar**, Kottayam, Kerala

Liv.52 gives excellent results to my patients. I treated a patient having alanine transaminase levels up to 187. After starting Liv.52, it reduced to 97 and the patient was cured. I am also prescribing Liv.52 to HIV positive patients, and getting good results.

**Dr Govindabhai Patel**, Mehsana, Gujarat
Book

Nutrition and Diet Therapy, Eleventh Edition

Editors: Ruth A Roth
Publisher: Delmar Cengage Learning, 2013
ISBN: 1133960502, 978-1133960508
Price: $139.27
Length: 704 pages

“Nutrition and Diet Therapy,” Eleventh Edition is an updated introduction to the essentials of nutrition concepts, good health, and client care that will provide the reader with a solid foundation with regard to nutrition. This book addresses misconceptions presented by the media as regards the link between good nutrition and good health, and also more effectively helps improve the nutrition and overall health of the reader.

This book is organized on the basis of 3 simple concepts: section 1 covers the fundamentals of nutrition, section 2 explains how to maintain good health through nutrition, and section 3 addresses the nutrition therapy concepts. It concludes that UNICEF and the World Bank, with their complementary approaches and in partnership with countries and other agencies, should initiate a global effort toward eliminating nutritional deprivation forever.

Online

American Society for Nutrition

http://www.nutrition.org/

Accessed on October 17, 2012

The American Society for Nutrition (ASN) is a nonprofit organization dedicated toward bringing together the world’s top researchers, clinical nutritionists, and industries to advance the knowledge and application of nutrition. The focus of the organization ranges from the most critical details of research and application to the broadest applications in society, in the United States and around the world.

ASN was founded in 1928 as the American Institute for Nutrition. Today, the Society encompasses both research and clinical foci and is building upon its 80-year-old rich history.

ASN is a constituent society of the Federation of American Societies for Experimental Biology (FASEB). Through excellence in nutrition research and practice, members of ASN enhance scientific knowledge and quality of life.
Quiz Corner

Crossword 11

Across
4. The unit of energy that indicates the amount of energy contained in food (7)
6. The nutrient needed to build strong bones (7)
7. The mineral that is essential for healthy red blood cells, whose deficiency might cause anemia (4)
8. The nutrient that is the preferred energy source for the body (13)
10. The nutrient needed to build and maintain the structural components of the body (7)

Down
1. The vitamin produced naturally by your body when exposed to sunlight and found in oily fish (8)
2. Citrus fruits are excellent sources of _________ (8)
3. This nutrient is most important for healthy vision (8)
5. The vitamin abundant in almonds (8)
9. The vitamin needed to prevent a birth defect called spina bifida (6)

Answers to Crossword 9 (Vol. LII No. 3 Apr-Jun 2012)

Down 1) HiOra Shine 3) Pencolax 4) Shallaki 5) PartySmart
Multiple micronutrient nutrition is an idea that originated in the 1940s and exemplifies the iterative nutritional paradigm. In the first 4 decades of the 20th century, scientists sought to segregate and characterize the vitamins that were responsible for xerophthalmia, rickets, pellagra, scurvy, and beriberi. In the early 1940s, studies were instituted to determine the dietary micronutrient requirements. Surveys showed that multiple micronutrient deficiencies were widespread in industrialized countries and the problem was addressed using cod-liver oil, iodized salt, fortified margarine, multiple-micronutrient fortified flour, and other foods of animal source.

After World War II, surveys showed that multiple micronutrient deficiencies were widespread in developing countries. Approaches to the elimination of multiple micronutrient deficiencies include periodic supplementation of vitamin A, iodized salt, targeted iron/folate as required; use of fortified flour, home-fortified micronutrient powders, other fortified foods; and adoption of homestead food production. Prevention of multiple micronutrient malnutrition is the key to achieving the Millennium Development Goals, given the important effects of micronutrients on health and survival.

This review is a journey back in timeline to find the prototypes of the various nasal specula around the beginning of 20th century. The oldest prototype, the tubular nasal speculum is documented in the ancient Hindu text Sushruta Samhita (6th century BC). The bivalved forceps-like nasal speculum was mentioned by Hippocrates and can be followed with and without self-retaining mechanisms to the modifications of Killian and Cottle.

U- or Y-shaped spring-like devices to open the nares have been known since the publication of Arnold de Villanova from the 13th century. They were reintroduced in a modification by Thudichum in 1868. Fraenkel’s speculum (1872) combines fenestrated blades with a self-retaining screw arrangement; Duply (1868) modified the split and funnel-shaped ear speculum of Bonnafont, in which the branches can be varied by a screw. In addition to this description of the prototypes of specula, a short development of the facilities to illuminate the inner nose is given starting with sunlight and ending with glass fiber optic.
Occasionally, you might try to sneak out between patients to survey the waiting room. Clinic day is never pleasant for the surgical intern, and you always hope that maybe no one else will show up. Maybe there is a blizzard and everyone decides it is just too dangerous to go outside, usually not though, and you peek through the Staff Only door around the corner from the physicians’ restroom and the free coffee to count the lineup. Every hour or so you may reassess the arrangement of the patients seated comfortably on their cushioned chairs, 18 more... 12… 7 …, then home. Clinic is not unbearable, but it only resembles what you think of when you think of medicine and try to remember why you wanted to become a physician in the first place. There is no real detective work, no mystery. Almost all patients who come to the clinic usually come with computed tomography (CT) scans and full workups and diagnoses already assigned by their primary physician. There is barely any examination to do and you almost always know exactly what the story is from the chart on the door: Patient referred by primary physician for (fill in diagnosis) requiring surgery.

From here the surgery intern does what he knows best: Paperwork. There are instructions to go over and over and sign and review again. After 45 min, the attending personnel may or may not appear, announce the time in his schedule when the case can be slotted in, and then quickly retreat to his office where he can complain about how little he will be paid for the procedure you just spent an hour arranging. So goes a clinic day in the large metropolitan city of US.

Transfer the same surgical intern from the climate-controlled architecture of the modern US city to a sweltering cinderblock box. Transfer to this village and its adjacent camp of refugees recovering from what the United Nations called the most brutal civil war of the 90s. You are now in Sierra Leone, not far from the Liberian border (where another brutal civil war just officially ended), and you are once again on a clinic day. Herein, you are not a surgical intern anymore, you are the doctor and you are not here to do paperwork as when you arrive in the morning, there are 50 starving women hovering over emaciated infants, waiting for you. They live next door in the camp, away from the relative wealth of the devastated subsistence agricultural economy in the village. They are the ones lucky enough to have walked here from the Mano River without being killed by the Liberian army, Sierra Leonean army, rebels, local militia, or the gangs of armed children that sprout like weeds in any country that survives a “brutal civil war.” The cinderblock box has 2 rooms and you set up your pharmacy in the first room. The pharmacy is donated by well-meaning persons who gather supplies from other well-meaning persons in the United States and other Western countries. It contains many lifesaving items such as antibiotics, antimalarials, and rehydration salts. It also contains many useless items such as colostomy supplies and Chapstick. You set up your office in the second room, with a small wooden desk, a steel basin of well water, a keg of soap, a small bag of disposable scalpels, lidocaine, a flashlight, and some gauze pads, although you are not sure of what you are supposed to do with any of it, and the sea of rags and bone swells on the broken benches waiting outside your room.

There is no chart, no referral from a primary physician, no primary physician, and no diagnosis neatly packaged and ready to be checked off on the office visit face sheet. Patients file into the 6 × 6 room and present themselves at a tiny desk behind which sits the doctor, fresh and white and reeking of health. Sometimes the translator can help decipher what the Sierra Leonean villagers are saying, cobbling together enough Mende or Krio to get out a rough history. Individual histories are impossible to ascertain, therefore from the collective story you need to guess. There are
no translators for the Liberians. You have seen the empty rice sacks and corrugated tin, which frames their houses as well as the grids of sewage that forms their property lines. You have tasted the cassava pap and fetid water that keeps them (barely) alive. You have bathed yourself in designer chemicals and prophylactic antimalarials to fend off the swarms of insects that are the only creatures to have found a paradise here among the sweat and heat and excrement of so many disrupted lives. The path that most took to get to the camp can be estimated from the same stories that we know from other brutal civil wars. Accused of being rebels by the military and being military by the rebels, these particular Liberians faced a very simple choice: Vacate the area for an uncertain future in an unknown place along an unsafe route or stay and die for sure by the hands of whichever group that decides to murder everyone in the village.

A mother walks in cradling her half-dead child in layers of filthy blankets. The child wears a diaper made from a frayed dishrag and a torn plastic bag. The dark yellow eyes of the mother, stained by malaria and unrelenting dust, reveal yet another story of suffering and desperation. You do not need a translator to see the fear in the eyes of a young mother. In addition, you do not need words to make you understand that she is saying “I am hungry and sick and my child is hungry and sick and we have nothing and nowhere to go and please help us because even as miserable as this existence seems we still don’t want to die today.”

The child is on fire. The skin, marred by superinfected weeping scabies, looks shrink-wrapped around a toy-store skeleton. The muddy eyes barely move and the child does not make a sound as you poke it and roll it over and squeeze the chest to appreciate the raging pneumonia. She weighs 12 or 15 pounds. There is no scale and there is no one who can predict her age. She does not look like she will get much older. She seems destined to become one of the 240 out of 1000 here who do not reach the age of 1 year. You can treat malaria, worms, and pneumonia. You can cure scabies. You can bring down the fever. We have all these medicines and the mother will get them all today. With pantomime and broad gestures, we will try to explain which medicines to be taken when. Pills given for malaria should be crushed and taken with pap, syrup should be taken for fever and pneumonia, and creams given should be spread on the scabies. The mother will get everything we can give — from chloroquine to Chapstick. And she will be shuffled out followed by the next ghost with her half-dead baby and her malaria, cataracts, malnutrition.

The acutely ill patients are in some way the easiest to see. Typhus and malaria can be treated. Parasites can be cured with 1 dose of medicine that costs less than a quarter. Diseases are easy. Life in a refugee camp is not. The children without pneumonias, the mothers without malaria, and the fathers with nothing more pathological than a lack of food are the most troubling. There is no cure for them as there is nothing that you can pack in a bag and dole out from your makeshift pharmacy.

To be a doctor here for even a day brings you face-to-face with the ordinary brutality of a life filled with hunger, violence, and hopelessness. You are faced, too, with the insignificance of everything you have learned and forced to rethink the illusion of power you may have once felt at being able to cut someone open, fiddle around a bit, and put him back together. One day in a clinic, a few kids were lucky enough to sufficiently get disinfectected and were sent back to their tin shacks to slug it out a little longer. A few mothers were, thus, relieved of having to watch their children die. For now.

Occasionally, you might try to sneak out between patients to see what kind of dent you are making in the line of 50 that started in the morning. Here, the clinic is sometimes overwhelming and you hope that maybe a freak rainstorm will keep everyone away for the rest of the day. You peek out of the suffocating cinderblock room to see the herd of bones, stiff and limping, littering the broken benches, and spilling onto the cement floor, say a 100 or 150. They keep streaming in, dreaming that you have some magic that will make it all better, counting on their faith in the doctor just as you have been losing yours. Off to the side, from your window you see under a dying tree in the sunbaked dust the Liberian woman, holding on desperately to her infant with the same stained eyes, eating a tube of Chapstick.

Laughter, the Best Medicine

A man suffered a serious heart attack and underwent open heart bypass surgery. He awakened from the surgery to find himself in the care of nuns at a Catholic hospital.

As he was recovering, a nun asked him questions regarding how he was going to pay for the services. She asked if he had health insurance.

He replied, in a raspy voice, “No health insurance.”

The nun asked if he had money in the bank.

He replied, “No money in the bank.”

The nun asked, “Do you have a relative who could help you?”

He said, “I only have a spinster sister, who is a nun.”

The nun got a little perturbed and announced loudly. “Nuns are not spinsters! Nuns are married to God.”

The patient replied, “Send the bill to my brother-in-law.”

As he lay on his deathbed, the man confided to his wife, “I cannot die without telling you the truth. I cheated on you throughout our whole marriage. All those nights when I told you I was working late, I was with other women. And not just one, but I’ve been with dozens of them.”

His wife looked at him calmly and said, “Why do you think I poisoned you?”

A customer sent an order to a distributor for a large amount of goods totaling a great deal of money.

The distributor noticed that the previous bill hadn’t been paid. The collections manager sent the customer a voice-mail saying, “We can’t ship your new order until you pay for the last one.”

The next day the collections manager received a phone call from the customer, “Please cancel the order. We can’t wait that long.”

Engineer’s terms and expressions…What they say (What they mean)

A number of different approaches are being tried (We are still guessing at this point)

Engaged in project coordination (We sat down and had coffee together)

Test results were extremely gratifying! (Unbelievable, it actually worked!)

The entire concept will have to be abandoned (The only guy who understood the concept has quit)

It is in process (It is so wrapped in red tape that the situation is completely hopeless)

We will look into it (Forget it! We have enough problems already)

See me/let’s discuss (Come to my office, I’ve messed up again)

I didn’t get your e-mail (I haven’t checked my e-mail for days)

Fax me the data (I’m too lazy to write it down)
Tentex Royal® (CAPSULE)
Enhances desire and improves performance

- Increases testosterone levels – Improves desire
- Enhances blood flow to the penile tissues – Improves erection
- Effective in ED of varied etiology
- Ensures satisfactory coitus
- Non-hormonal & safe
- No risk of priapism, blindness, or fibrosis

Indication:
Erectile dysfunction

Dosage
2 capsules once daily, one hour before sexual intercourse, for 6 to 12 weeks.
It is necessary to continue the treatment for a minimum of 6 weeks without interruption for satisfactory correction of erectile dysfunction.

Tentex Royal®
Enhances desire and improves performance

In the management of erectile dysfunction...
Introducing shortly

HiOwna®

A balanced, natural, nutritional health drink that promotes overall health and well-being in adults and elderly.

Nutrition and good health... Naturally!

- **A natural, nutritional health drink** especially formulated for senior adults, hospitalized adults, and multitasking adults
- **Fortified with pea protein**, soy protein isolate, skimmed milk powder, essential vitamins and minerals that supplement the daily diet
- **Helps faster recovery** from prolonged illnesses like cancer, tuberculosis, typhoid, and stroke
- **The herbal actives** present in HiOwna:
  - Help build a strong immune system that prevents repeated infections
  - Help adapt to stressful conditions with ease
- **Free from cholesterol**, trans fats and saturated fats, which makes it safe for cardiac and dyslipidemic patients
- **Easily digestible**, does not cause bloating
- **Manufactured by a unique process**, which makes it easy to disperse

**Indications**
As a daily nutritional health drink supplement for adults and elderly, and also in:
- Postoperative convalescence
- Prolonged illness
- Stress of varied etiology

**Dosage**
4 heaped tablespoons (approx. 25g) twice daily.

**Serving instructions:**
- Take a cup of lukewarm/cold milk or water
- Add 4 heaped tablespoons (approx. 25 g) of HiOwna
- Stir briskly until mixed well
- Add sugar to taste, if required.

The Himalaya Drug Company
Makali, Bangalore 562 123, India
www.himalayahealthcare.com
E-mail: write.to.us@himalayahealthcare.com