A Standardized *Withania Somnifera* Extract Significantly Reduces Stress-Related Parameters in Chronically Stressed Humans: A Double-Blind, Randomized, Placebo-Controlled Study

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ABSTRACT

*Withania somnifera* (WS) has historically been used in Asia for treating stress-related health conditions. In this study, we investigated the effects of standardized WS root and leaf extract (WSE) in chronically stressed humans in a modern clinical trial. Participants were randomly assigned to WSE (125 mg QD, 125 mg BID, or 250 mg BID) or placebo groups. Stress levels were assessed at Days 0, 30, and 60 using a modified Hamilton anxiety (mHAM-A) scale. Biochemical and clinical variables were measured at Days 0 and 60. Of 130 subjects enrolled, 98 completed the study. Between Days 0 and 60, the WSE 125 mg QD group decreased significantly more than placebo for mean mHAM-A score, serum cortisol, serum C-reactive protein, pulse rate and blood pressure, and increased significantly for mean serum DHEAS and hemoglobin. Other WSE treatment groups had greater dose-dependent responses in these parameters and had significantly greater responses compared to placebo in mean fasting blood glucose, serum lipid profiles and cardiac risk ratios. Participants and dropouts reported no adverse effects. Therefore, this study provides evidence that the consumption of WSE significantly reduces experiential and biochemical indicators of stress without adverse effects.

Key words: *Withania somnifera*, antistress, withanolides, sitoindosides, cortisol, C-reactive protein.

INTRODUCTION

Stress is a major component of modern life, causing adverse physiological conditions such as cognitive deficiencies, impaired glucose and lipid homeostasis, immunosuppression, sexual dysfunction, gastric ulceration, and alteration in serum cortisol and dehydroepiandrosterone sulfate (DHEAS) levels. Development of active management and treatment protocols that control stress-related symptoms with minimum adverse effects would be of great benefit.

*Withania somnifera* Durai (Solanaceae) (WS) has traditionally been used in Asia for safely managing and treating stress. Also known as Ashwagandha, Indian ginseng and winter cherry, it belongs to a *rasayana* (vitalizer) group of medicinal plants that stabilize and revitalize systemic functions. The Ayurvedic system of medicine claims that it promotes stress relief, health and longevity by potentiating the immune system, arresting premature aging, restoring homeostasis and increasing resistance to adverse environ-
mental factors, collectively known as the antistress-adaptogenic effect. However, its healing effects on chronically stressed individuals have never been evaluated in a randomized, controlled clinical trial.

Several bio-actives, including withanolide glycosides (also known as sitoindosides) and withanolide aglycones, are considered to be responsible for the medicinal properties of WS. Traditional medicinal use of WS has employed root powder derived from wild plants, which are relatively low in concentration of bioactives. Cultivated WS varieties differ morphologically from wild WS, and have higher levels of bioactive components. Methods to further concentrate levels of bioactives in standardized WS extracts (WSE) have also been developed.

The objective of this study was to investigate, in chronically stressed adults, the impact of WSE on experiential and biochemical indicators of stress and anxiety as well as cardiovascular risk, and to evaluate WSE tolerance.

MATERIALS AND METHODS

This double-blind, randomized, placebo-controlled study was conducted from November 2004 to October 2006 at the Central Research Institute (Ayurveda), Ministry of Health and Family Welfare, Bidhan Nagar, Kolkata, India (CRI), in accordance with the World Health Organization's Guideline for Good Clinical Practice and the World Medical Association Declaration of Helsinki. The CRI Ethics Committee approved the protocol. Patients identified as stressed in the CRI outpatient department were assessed clinically (blood pressure, resting heart rate, reflexes, and neurological and psychological status) and completed a questionnaire assessing the severity of stress symptoms (cognitive, mood, and behavioral) based on a Bengali version of a modified Hamilton anxiety (mHAM-A) scale for stress.

In the questionnaire, patients rated symptoms of anxiety (fatigue, flushing, perspiration, loss of appetite, headache and muscle pain, feelings of impending doom, palpitations, dry mouth, sleeplessness, forgetfulness, irritability, and inability to concentrate) on a 5-point scale (0 = no symptoms; 1 = occasional; 2 = mild/poor; 3 = moderate; 4 = severe). The total score was calculated by adding the score from individual questions.

Men and women aged 18 to 60 years were eligible for the study if they had a mHAM-A score of 24 to 42. Exclusion criteria were any concomitant serious physical disorder(s) or antistress treatment (antidepressants, anxiolytic) that was ongoing or had occurred during the previous month. Exercise as well as drugs that lower serum lipids, blood pressure or blood sugar were not considered exclusion criteria, but this was not considered a significant bias in the study because only two participants (1.5% of the total) were taking drugs of this nature (hypertensive) and they were allocated randomly into different treatment groups. Participants provided written informed consent in English and Bengali, the local language, and were randomly divided into four groups using a computer-generated random number list: WSE 125 mg QD, WSE 125 mg BID, WSE 250 mg BID, and placebo.

The WSE used in this study (trade names Sensolax, NutraGenesis, LLC, Brattleboro, Vermont) was derived from a withaniferin A and corresponding withanolide glycoside-predominant, genetically uniform chemotype, which was cultivated in the central and northern provinces of India. WS root and leaf material was processed using a water-based extraction protocol and assessed using high performance thin layer chromatography analysis of fractions against standard references (CAMAG Linomat V applicator, CAMAG TLC Scanner, and WinCats software version 1.3.4; CAMAG, Sonnenmattstr. Muttenz, Switzerland) in accordance with US Patent 6,713,092. The single lot of WSE used in the study had a composition of 11.90% withanolide glycosides, 1.05% withaniferin A, 40.25% oligosaccharides, 0.05% alkaloids, and 3.44% polysaccharides with no scopamine, pyrrolizidine alkaloids or aristolochic acid.

WSE (125 mg or 250 mg) plus excipients or excipients only (placebo) were placed in coded hard-gelatin capsules identical in size, shape, color (opaque white) and texture. Participants received two bottles of capsules and were told to take one capsule from Bottle 1 before lunch and one capsule from Bottle 2 before dinner for 60 days. Participants in the WSE 125 mg QD group took a 125 mg WSE capsule before lunch and a placebo capsule before dinner. Participants in the other groups took two of the same capsule (corresponding to the group name, e.g., the placebo group took two placebo capsules, etc.) each day. At each of four visits, participants received a 15-day supply of capsules. Compliance was monitored by counting the remaining pills at each follow-up visit and at the end of the study. Information about tolerance (i.e., treatment-emergent adverse effects) was obtained by questioning the participants and clinically examining them at each visit.

Experiential feelings of stress and anxiety were assessed by calculating the sum of scores from the mHAM-A questionnaire taken at baseline (Day 0). Day 30 and Day 60. To measure biochemical markers of stress and anxiety, participants fasted overnight prior to visits at baseline and Day 60 to avoid diurnal variations (particularly in serum cortisol concentration). Blood samples (6–10 mL) were collected in vacutainer tubes (BD Vacutainer Systems, Plymouth Devon, UK) between 9 a.m. and 11 a.m., stored at 4°C, and assayed for serum concentrations of cortisol, dehydroepiandrosterone sulfate (DHEAS), C-reactive protein (CRP), fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), and alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), creatinine kinase (CK), and uric acid (UA) levels.
lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), and hemoglobin at a laboratory (Doyen Diagnostic & Research Foundation, 59 Bhupen Bose Avenue, Kolkata-700004) accredited by the National Accreditation Board for Testing and Calibration Laboratories, Dept. of Science and Technology, Government of India. Pulse rate and blood pressure were also determined.

Difference scores were calculated by subtracting sum values at 30 days from baseline, 60 days from baseline, and 60 days from 30 days for each variable individually and for the total anxiety score. Difference scores were then compared among groups using 1-way analyses of variance with post hoc pairwise comparisons of the three treatment groups with the placebo group using the least significant difference method. Percent changes were expressed as the difference between the means of the baseline and treatment phases divided by the mean of the baseline phase multiplied by 100. Cardiovascular risk ratios (TC:HDL-C and LDL-C:HDL-C) were calculated as TC divided by HDL-C and LDL-C divided by HDL-C, respectively. Values between 3.5 and 5 for TC:HDL-C and between 1.1 and 3.6 for LDL-C:HDL-C indicate average risk of developing coronary artery disease and heart disease. Sample size calculations were not done for this study. \( P < 0.05 \) was considered statistically significant.

RESULTS

Out of 160 eligible participants, 130 (95 men, 35 women; mean age=39.8 years) initially enrolled in the study (Table 1) and 32 (26 men, 6 women) dropped out (WSE 125 mg QD group, 11; WSE 125 mg BID group, 5; WSE 250 mg BID group, 1; and placebo group, 15). Reasons for study withdrawal were protocol violations, 6; being lost to follow-up, 10; physician's decision, 4; and lack of efficacy, 12. This dropout rate (and the fact that lack of efficacy was the largest category of dropouts) is fairly common in clinical trials of psychiatric drugs and is well within professionally recognized limits. Because dropouts were not included in the final analysis, per-protocol analysis was followed and intent-to-treat analysis was not performed.

Participants in all WSE treatment groups experienced improved well being at Day 30 and Day 60 (Figure 1). The 125 mg QD group decreased significantly \( (P<0.001) \) in mean sum mHAM-A score from baseline (29.9) to Day 30 (18.1; -39.5%) and to Day 60 (11.3; -62.2%) compared to the placebo group, which showed no significant mean change in sum mHAM-A score throughout the study. Mean sum mHAM-A scores for the other WSE groups decreased even further than for the 125 mg QD group in a dose-dependent manner. The mean sum mHAM-A score for the placebo group at baseline, 27.6, was lower than those of the WSE-treated groups (which ranged between 29.2-29.9), but not significantly. Mean scores for individual questions on the mHAM-A questionnaire also decreased significantly \( (P<0.001) \) at Day 30 and Day 60 for all WSE treatment groups versus the placebo group (Table 2).

Mean values (SD) of biochemical and clinical parameters investigated for each treatment group are summarized in Tables 3 and 4. Between baseline and Day 60, the WSE 125 mg QD group decreased significantly \( (P<0.05) \) more than the placebo group for mean serum cortisol (+14.5%), serum VLDL-C (-8.9%), systolic BP (-1.6%), diastolic BP (-5.6%), and \( (P<0.001) \) serum CRP (+31.6%) and pulse rate (-6.0%), and increased significantly \( (P<0.05) \) more than the placebo group for mean serum DHEAS (13.2%) and hemoglobin (6.3%). For the same period, the other WSE treat-

<table>
<thead>
<tr>
<th>Characteristic, Group</th>
<th>WSE 125 mg QD (n = 30)</th>
<th>WSE 125 mg BID (n = 35)</th>
<th>WSE 250 mg BID (n = 35)</th>
<th>Placebo (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>37.8 (12.4)</td>
<td>39.4 (12.6)</td>
<td>40.0 (9.9)</td>
<td>42.1 (9.6)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>22 (73.3)</td>
<td>27 (77.1)</td>
<td>23 (65.7)</td>
<td>23 (76.7)</td>
</tr>
<tr>
<td>Women</td>
<td>8 (26.7)</td>
<td>8 (22.9)</td>
<td>12 (34.3)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>58.9 (9.9)</td>
<td>60.5 (9.0)</td>
<td>59.1 (9.2)</td>
<td>59.1 (6.6)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>161.8 (9.3)</td>
<td>161.5 (7.7)</td>
<td>162.7 (7.3)</td>
<td>159.4 (6.7)</td>
</tr>
</tbody>
</table>

WSE = Withania somnifera extract.

* No significant between-group differences were found.
Table 2. Mean (SD) scores by treatment group for individual symptoms of stress and anxiety based on a modified Hamilton anxiety scale at Day 0 (baseline) and after 30 and 60 days of treatment with *Withania somnifera* extract (WSE) or placebo (n = 98).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Fatigue</th>
<th>Flushing</th>
<th>Perspiration</th>
<th>Loss of appetite</th>
<th>Headache and muscle pain</th>
<th>Feelings of impending doom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Day 0</td>
<td>Day 30</td>
<td>Day 60</td>
<td>Day 0</td>
<td>Day 30</td>
<td>Day 60</td>
</tr>
<tr>
<td>WSE 125 mg QD</td>
<td>3.2</td>
<td>1.8</td>
<td>2.1</td>
<td>2.4</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>(n = 19)</td>
<td>(0.7)</td>
<td>(0.3)</td>
<td>(1.6)</td>
<td>(0.3)</td>
<td>(0.3)</td>
<td>(0.6)</td>
</tr>
<tr>
<td>WSE 125 mg BID</td>
<td>2.9</td>
<td>1.3</td>
<td>1.6</td>
<td>1.9</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>(n = 30)</td>
<td>(0.9)</td>
<td>(1.1)</td>
<td>(0.9)</td>
<td>(1.1)</td>
<td>(0.7)</td>
<td>(0.6)</td>
</tr>
<tr>
<td>WSE 250 mg BID</td>
<td>3.0</td>
<td>1.4</td>
<td>1.8</td>
<td>1.8</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>(n = 34)</td>
<td>(1.0)</td>
<td>(0.8)</td>
<td>(1.0)</td>
<td>(1.0)</td>
<td>(0.4)</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.9</td>
<td>2.9</td>
<td>1.9</td>
<td>1.5</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>(n = 15)</td>
<td>(0.9)</td>
<td>(0.8)</td>
<td>(0.8)</td>
<td>(0.9)</td>
<td>(0.5)</td>
<td>(0.8)</td>
</tr>
</tbody>
</table>

\* Scale: 0 = never; 1 = occasional; 2 = mild/poor; 3 = moderate; 4 = severe.

\( \uparrow P < 0.01 \) versus Placebo Group, \( \uparrow\uparrow P < 0.05 \) versus 30 days of treatment.

ment groups had even greater responses in these parameters than the WSE 125 mg QD group in a dose-dependent manner. In addition, the WSE 125 mg BID group had significantly (P<0.05) greater reductions, compared to the placebo group, in mean FBG (-4.7%), serum TC (-7.0%), serum TG (-9.5%), and serum LDL-C (-9.0%). The WSE 250 mg BID group had similar greater responses in mean FBG, and serum TC, TG and LDL-C than the WSE 125 mg BID group, and also had a significantly (P<0.001) greater increase in mean serum HDL-C compared to the placebo group (17.3%). Cardiac risk ratios, at the higher end of the average risk range at Day 0 for all treatment groups, improved for the two higher dosage WSE groups at Day 60 by decreasing significantly (P<0.05) compared to the placebo group (data not shown).

No significant difference was observed in the placebo group between baseline and Day 60 for any biochemical or clinical parameter measured. In addition, no study participant or dropout experienced any adverse effects or withdrawal effects, regardless of the dosage or frequency.

### DISCUSSION

Several studies have been carried out during the last few decades on the chemical constituents of WS and its biological activities, mostly using powder (or non-standardized extracts) derived from the roots of wild plants. Experimental studies of WS have assessed its antistress, antioxidant, immunomodulatory, anticancer, tumor, cardioprotective, antiosteoarthritis and antiaging activities. Our study is the first to evaluate the therapeutic benefits of standardized WSE in human subjects using modern clinical trials.

Our findings that WSE reduces experiential feelings of stress and anxiety at all dosage levels tested supports the traditional claims of WS's antistress-adaptogenic effect. All WSE-treated groups showed improvement in mHAM-A stress and anxiety scores at both Day 30 and Day 60 as a result of participants feeling less fatigue, flushing, perspiration, loss of appetite, headache and muscle pain, feelings of impending doom, palpitations, dry mouth, sleeplessness, for-
Table 3. Mean (SD) values and percentage changes by treatment group of biochemical variables measured at Day 0 (baseline) and after 60 days of treatment with *Withania somnifera* extract (WSE) or placebo (n = 98).

<table>
<thead>
<tr>
<th>Biochemical Variables</th>
<th>Serum Cortisol (µg/dL)</th>
<th>Serum DHEAS (µg/dL)</th>
<th>CRP (mg/L)</th>
<th>FBG (mg/dL)</th>
<th>Serum TC (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Day 0</td>
<td>Day 60</td>
<td>%Δ</td>
<td>Day 0</td>
<td>Day 60</td>
</tr>
<tr>
<td>WSE 125 mg QD (n = 19)</td>
<td>13.1</td>
<td>11.2</td>
<td>-14.5</td>
<td>167.4</td>
<td>180.5</td>
</tr>
<tr>
<td>WSE 250 mg BID (n = 30)</td>
<td>12.8</td>
<td>9.7</td>
<td>-24.2</td>
<td>152</td>
<td>200.7</td>
</tr>
<tr>
<td>Placebo (n = 15)</td>
<td>13.5</td>
<td>14.1</td>
<td>4.4</td>
<td>165.7</td>
<td>140.3</td>
</tr>
</tbody>
</table>

DHEAS = dihydroepiandrosterone sulfate; CRP = C-reactive protein; FBG = fasting blood glucose; TC = total cholesterol; TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; VLDL-C = very low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol. * P<0.05 versus Placebo Group; † P<0.001 versus Placebo Group; ‡ P<0.05 versus WSE 125 mg QD Group, # P<0.05 versus WSE 125 mg BID Group.

getfulness, irritability and inability to concentrate. The placebo group did not display changes in mHAM-A score throughout the study. Feelings of frustration that treatment was not helping their stress may have contributed to the higher dropout rate in this group. The placebo group had nine participants drop out due to lack of efficacy compared to three for all WSE-treated groups combined (data not shown).

WSE’s therapeutic activity may be attributed, at least in part, to its effect on the hypothalamic-pituitary-adrenal axis, which regulates serum cortisol concentration.28 The link between adaptogenic effects and cortisol has previously been described.29 In fact, the mean serum cortisol concentration in all three WSE-treated groups, while being in the normal range throughout the study, declined between baseline and Day 60. In individuals with normal circadian rhythm, serum cortisol concentration is high in the morning and tends to decrease throughout the afternoon, reaching its lowest point around 11 p.m.30 One of the effects of chronic stress is that serum cortisol concentration peaks in the afternoon, rather than becoming lower.28 Supplementation with WSE may offset this afternoon cortisol peak in stressed individuals, although future studies are needed to confirm this.

**Figure 1.** Mean sum (SD) total stress and anxiety scores based on a modified Hamilton anxiety (mHAM-A) scale2 by group for Day 0 (baseline), Day 30 and Day 60 of treatment with *Withania somnifera* extract (WSE) or placebo (n = 98).

![mHAM-A Score Chart]

- WSE 125 mg QD (n=19)
- WSE 125 mg BID (n=30)
- WSE 250 mg BID (n=34)
- Placebo (n=15)

Scale: 0 = never; 1 = occasional; 2 = mild/poor; 3 = moderate; 4 = severe.
Table 4. Mean (SD) values and percentage changes by treatment group of clinical variables measured at Day 0 (baseline) and after 60 days of treatment with Withania somnifera extract (WSE) or placebo (n = 98).

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Hemoglobin g/dL</th>
<th>Pulse rate Beats/min</th>
<th>Systolic Blood Pressure (BP) mm Hg</th>
<th>Diastolic Blood Pressure (BP) mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 60</td>
<td>%Δ</td>
<td>Day 0</td>
</tr>
<tr>
<td>WSE 125 mg</td>
<td>12.7</td>
<td>13.5</td>
<td>6.3†</td>
<td>76.4</td>
</tr>
<tr>
<td>QD (n = 19)</td>
<td>(1.2)</td>
<td>(1.5)</td>
<td></td>
<td>(4.6)</td>
</tr>
<tr>
<td>WSE 125 mg</td>
<td>12.6</td>
<td>13.1</td>
<td>4.0†</td>
<td>80.7</td>
</tr>
<tr>
<td>BID (n = 30)</td>
<td>(1.3)</td>
<td>(1.4)</td>
<td></td>
<td>(6.4)</td>
</tr>
<tr>
<td>WSE 250 mg</td>
<td>12.1</td>
<td>13.2</td>
<td>9.1†</td>
<td>78.8</td>
</tr>
<tr>
<td>BID (n = 34)</td>
<td>(1.2)</td>
<td>(1.1)</td>
<td></td>
<td>(7.7)</td>
</tr>
<tr>
<td>Placebo</td>
<td>12.7</td>
<td>12.5</td>
<td>−1.6</td>
<td>78.4</td>
</tr>
<tr>
<td>(n = 15)</td>
<td>(1.2)</td>
<td>(1.2)</td>
<td></td>
<td>(2.3)</td>
</tr>
</tbody>
</table>

* P<0.05 versus Placebo Group, † P<0.001 versus Placebo Group.

concentration, which can be used as a marker of stress. In the present study, the WSE-treated groups displayed increased serum DHEAS concentrations by the end of the study, compared to the placebo group. The normalizing action of WSE may also be due to neuroprotective properties of withanolide glycosides and withaferin A that help reduce the stress-induced generation of reactive oxygen species in various parts of the brain.

Chronic stress has been found to be associated with higher than normal levels of serum CRP, a systemic marker of inflammation that is associated with increased risk for a host of chronic diseases. Use of WSE at all doses and frequencies in this study resulted in a decrease in mean serum CRP concentration, indicating that systemic inflammation may have declined in members of each WSE-treated group. Ingestion of WS root powder has decreased inflammation in animal models. Together these findings suggest that WSE use might contribute to decreased risk of chronic disease, an idea meriting further investigation.

Reduction in fasting blood glucose concentration in the two highest dosage WSE-treated groups was also found. This finding may be related to the observed concomitant reduction in serum cortisol concentration. Cortisol is a glucocorticoid hormone that performs several functions, including regulation of blood sugar levels.

CONCLUSIONS

This study determined that daily consumption of standardized WSE at three dosages (125 mg QD, 125 mg BID, and 250 mg BID) reduced experiential feelings of stress and anxiety, serum concentrations of cortisol and CRP, pulse rate and blood pressure; and increased serum concentration of DHEAS in the chronically stressed adults who completed the study. The WSE 125 mg BID and WSE 250 mg BID dosages also improved fasting blood glucose levels and lipid profiles for study participants in those groups. Cardiac risk ratios improved for the two higher dosage WSE groups. Although the 25% dropout rate may have partially skewed results, the observed dose-dependent, significant trends in most variables evaluated support the view that daily use of WSE would benefit people suffering from the effects of stress and anxiety without any adverse effects.

ACKNOWLEDGMENT

We would like to thank Natren Inc. (New Brunswick, New Jersey) for financial support of this study.

POTENTIAL CONFLICTS OF INTEREST

Dr. Auddy is an employee of Natren Inc., which is the patent holder of Withania somnifera extract sold under the trade names Essentra® and Sensoril®.

Dr. Abedon is an employee of NutraGenesis LLC, which sells Withania somnifera extract exclusively under the trade names Essentra® and Sensoril®.

Dr. Ghosal was an unpaid adviser to Natren Inc. at the time the study was conducted.
REFERENCES


