

Research

Effects of a Modified Yeast Supplement on Cold/Flu Symptoms

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Immune modulation that includes suppression or enhancement of immune function has become either a primary or potential form of adjuvant preventive medical treatment, and is an ongoing focus of research (Ault, 2007; Chiarella, Massi, DeRobertis, Signon, & Fazio, 2007). For example, immune suppression is utilized for more complex diseases, such as rheumatic arthritis, asthma, and inflammatory bowel disease (Leath, Singla, & Peters, 2005; Williams, Paleolog, & Feldmann, 2007). Other conditions, such as allergic reactions, also require down-regulation of immune function, usually with less intensity, and numerous over-the-counter treatments are

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A yeast-based product (EpiCor®, a dried Saccharomyces cerevisiae fermentate) was compared to placebo to determine effects on the incidence and duration of cold and flu-like symptoms in healthy subjects recently vaccinated for seasonal influenza. In a 12-week, randomized, double-blind, placebo-controlled clinical trial, 116 participants received daily supplementation with 500 mg of EpiCor or placebo for 12 weeks. Data collected included periodic in-clinic examinations and serologic evaluations at baseline, 6- and 12-weeks. Subjects also utilized a standardized self-report symptom diary during the study. Participants receiving the yeast-based product had significantly fewer symptoms and significantly shorter duration of symptoms when compared with subjects taking a placebo.

Key Words: Influenza, *Saccharomyces cerevisiae*, yeast, EpiCor, common cold, flu, dietary supplement.

Introduction

Many over-the-counter products claim to reduce symptoms associated with cold and flu. This is the largest randomized trial to date to examine the impact of a daily modified yeast-based product (EpiCor®, a dried *Saccharomyces cerevisiae* fermentate) compared to placebo on the incidence and duration of cold and flu-like symptoms in healthy subjects recently vaccinated for seasonal influenza.

Objective

To determine if a modified yeast-based dietary supplement (EpiCor) taken daily reduces the incidence and duration of colds or flu-like symptomatic features in a group of healthy individuals recently vaccinated against seasonal flu (influenza).

Design and Method

A 12-week experimental, double-blind, placebo-controlled study of 116 randomized, healthy participants with up-to-date vaccination histories received daily supplementation with 500 mg of EpiCor or placebo for 12 weeks. Clinical outcome measurements included periodic in-clinic examinations at baseline, 6- and 12-

weeks; participants also utilized a standardized self-report symptom diary during the entire study. Comprehensive laboratory serologic analysis was performed during each clinic visit.

Results

Subjects receiving EpiCor experienced a statistically significant reduction in the incidence ($p = 0.01$) and duration ($p = 0.03$) of colds or flu compared with participants receiving placebo. Additionally, subjects in the EpiCor group experienced a non-significant ($p = 0.23$) reduction in adverse events compared to placebo.

Conclusions

Daily nutritional supplementation with 500 mg of EpiCor may be an effective adjuvant preventive treatment in patients recently vaccinated for seasonal influenza. This yeast-based intervention also demonstrated a safety profile similar to a placebo. Future studies should focus on the use of this product as a potential single agent to reduce cold and flu-like symptoms in healthy individuals.

Level of Evidence – Level II

now available (Finegold, 2007). Enhancement of immune function also is being investigated currently as a potential primary form of medical treatment for certain types of invasive diseases, such as cancer (Cranmer & Hersh, 2007; Moyad, 2007a; O'Neill & Bhardwaj, 2007).

Respiratory infections are also part of an intense focus on better preventive therapies. Influenza is now responsible for more than 200,000 hospitalizations and approximately 36,000 deaths per year in the U.S. alone (Lynch & Walsh, 2007; Roxas & Jurenka, 2007; Zimmerman, 2005), and it is one of the top 10 causes of mortality in men and women.

However, the incidence and impact of this ever-changing viral infection is increasing, which is potentially due to the current and ongoing increase in the aging population. The seasonal vaccine itself has kept this disease from becoming a more primary cause of morbidity and mortality, and health education concerning the importance of this vaccine has been a critical component to effective preventive medicine. Concerns about vaccine resistance, waiting periods for novel annual vaccines, and patient access issues (regardless of financial background or insurance status) limit its use in many geographical areas and among different population groups.

The common cold is less of a medical concern; yet, virulent variants of the common cold are becoming more common. The lack of preventive treatment is perhaps one of the many reasons this class of virus is responsible for millions of dollars a year in the lack of productivity due to convalescence (Roxas & Jurenka, 2007).

Identifying effective adjuvant preventive therapies synergistic or complementary to conventional treatments may be beneficial in decreasing the symptoms and duration of influenza and colds. A simplistic or complex reasonably priced method that enhances general immune function and may reduce a variety of

infections or symptoms, including those of the common cold or influenza, seems to be a reasonable and ethical option to improve overall health outcomes, productivity, and general well being.

Objective

To date, many over-the-counter options claim significance as a potential adjuvant therapy or sole treatment for colds and flu-like symptoms, but few dietary supplements, apart from vitamin C, have had adequate numbers of clinical trials conducted (Moyad & Combs, 2007). For example, meta-analyses exist of randomized trials of vitamin C and its impact on pneumonia (Hemila & Louhiala, 2007) or the common cold (Douglas, Hemila, Chalker, & Treacy, 2007). More over-the-counter products should be subjected to rigorous double-blind randomized trials.

Saccharomyces cerevisiae, better known as baker's or brewer's yeast, has a long history of providing some form of immune protection or health promotion beyond its commercial applications (Moyad, 2007b). Modified forms of this species of yeast have been shown to be safe in moderate dosages but may provide enhanced immune benefits beyond what is typically capable in its original form. For example, one of the largest randomized trials of cancer prevention that showed benefits seemed to enhance selenium supplementation awareness, but the actual trial utilized a modified yeast form that included 200 mcg of selenium, as opposed to selenium by itself (Clark et al., 1996). Decades-old research shows that this same principle has already been applied to other forms of yeast, but the lack of randomized trials that included a placebo is one potential major limitation to determining whether or not yeast-based technology has a future in preventive medicine (Moyad, 2007b). Therefore, this research group decided to provide more clarity on this issue.

This randomized trial is the largest to date that has examined the impact of a yeast-based dietary supplement on the incidence of cold and flu-like symptoms, and more specifically, on the symptoms associated with these conditions in subjects with a recent history of seasonal influenza vaccination.

The primary objective of the study was to determine if a once-daily dose of the modified yeast product would reduce the incidence and duration of the common cold or influenza-like symptoms in healthy human subjects that had recently received the influenza vaccine. A second endpoint measured in the study was the severity of these symptoms if illness occurred.

Methods

Sample and setting. Individuals were recruited via print advertisements, local television, and e-mail. Age range was 18 to 76 years ($M = 44$, $SD = 11$) and included subjects living in a metropolitan area of the rural Midwest. The number of participants at the start of the study totaled 130. There were a total of 14 dropouts during the study, including 10 in the supplement group and 4 in the placebo group. The final analyses were carried out on the results from 116 participants.

Inclusion criteria. Selected individuals were healthy, with a Charlson comorbidity of 0 or 1 (Charlson, Szatrowski, Peterson, & Gold, 1994), based on basic physical examination by clinical and research staff and via self-report. All had recently received the seasonal influenza vaccine.

Exclusion criteria. Exclusion criteria are listed in Table 1.

Power Analysis

Power analysis was conducted prior to the study for the proposed sample size and significance level (0.05). Based on the proposed sample size with approximately a similar number of control subjects compared to the intervention group, the computed power is 0.886. This com-

Table 1.
Exclusion Criteria Utilized Before Determination of Randomization
in the Cold and Flu Study of the Modified Yeast-Based Product
Compared to Placebo

Diagnosed or treated immune abnormality
Current use of any immunosuppressive medication (such as azathioprine, cyclosporine, and steroids)
Current use of any antiviral medication (including amantadine, oseltamivir, rimantadine, and zanamivir)
HIV positive
ALT, AST, BUN, and/or creatinine laboratory values greater than 2 times the upper limit of normal
Females who are pregnant or breastfeeding, or who are planning to become pregnant during the study period
History of substance abuse
Severe co-morbidity or concomitant disease or condition
Allergies to yeast or to yeast-derived products
Environmental allergies requiring medication or allergy-based injection therapy
Vitamin deficiency that requires supplementation
Herbal or supplemental preparation use such as echinacea, vitamin C, or zinc
Received seasonal influenza vaccination for 2006 to 2007 period, and more than 60 days have elapsed between vaccination and the randomization period
Unable or unwilling to comply with the study protocol (including ingesting the study supplement or placebo, regular blood sampling, and completing the study diary)
Current participation in another clinical research investigation of any kind

putation results in an 88.6% probability of identifying a statistically significant difference between incidence rates for the control versus the intervention group, with a 0.05 significance, if a true difference exists. Final statistical analysis on the outcomes utilized a two-way analysis of variance (ANOVA), with EpiCor and placebo as treatment factor, and all symptoms as another factor. Ninety-five percent confidence intervals (95% CI) were calculated around each mean value to determine the appropriate range of accuracy within each separate clinical outcome.

Protection of human subjects. The clinical study was conducted in accordance with Good Clinical Practice (GCP) and all applicable regulatory requirements, and was approved by the Institutional Review Board (IRB) by the Avera Institutional Review Board (IRB) for Avera Health (Sioux Falls, SD).

Procedure

This 12-week, randomized, double-blind, placebo-controlled trial was conducted during the acute period of the year for cold and flu seasonal symptoms (December 2006 to March 2007). Individuals meeting the inclusion criteria and giving informed consent were screened for a maximum of 14 days to determine baseline standardized laboratory values, including complete blood count (CBC), complete metabolic profile, and other general health serologic parameters.

All forms of medications ingested by subjects during screening or the 12-week study period were recorded, and any changes in medications or dosages were also noted in the patient chart. Subjects were encouraged throughout the study to continue unaltered with their specific dietary regime, exercise, alcohol consumption, and all other behavioral patterns, includ-

ing smoking, throughout the study period.

Subjects were randomized to one of two groups. Both groups demonstrated statistical equivalence at baseline for body mass index, medication usage, and smoking status. The following mean baseline characteristics for the EpiCor and placebo group were: age (43 [$SD = 10$] and 45 [$SD = 13$] years, $p = 0.265$), BMI (27.8 [$SD = 6.6$] and 26.7 [$SD = 4.7$], $p = 0.283$), and current smoking status (14% and 20%); 57% of the participants were female. There was no statistical significance between baseline characteristics of either group. The experimental group ($n = 52$) received daily doses of 500 mg modified yeast-based product intervention (EpiCor); the control group ($n = 64$) received a placebo.

EpiCor is a dietary supplement, as defined by the Dietary Supplement and Health Education Act (DSHEA) of 1994 (U.S. Food & Drug Administration, 2007) and was developed by Embria Health Sciences, LLC., of Ankeny, IA. It consists of a fermented medium of *Saccharomyces cerevisiae*, which when proliferating under stress secretes multiple bioactive metabolites. Over the last 60 years, a feed additive product for commercial animals based on this proprietary technology has been utilized to enhance immune function and to prevent disease. Recently, the human-modified version of this product (EpiCor) has been subject to multiple laboratory safety, stability, and efficacy investigations. For example, EpiCor has demonstrated anti-inflammatory properties with the stimulation of B lymphocytes and natural killer (NK) cells (Jensen, Hart, & Schauss, 2007).

The placebo capsule was of a similar appearance, weight, and non-odor as the active intervention. Subjects were instructed to ingest medications with breakfast. Participants attended the research institute clinic at weeks 0 (baseline), 6, and 12, and in addition to examination, were required to record cold and flu-like symptoms at home in a modified standard-

Figure 1.
The Standardized Diary to Evaluate Incidence, Duration, and Severity of Cold and Flu-like Symptoms

As soon as you start noticing any symptoms of cold or influenza, please fill in the diary.

DATE _____	No symptoms	Please assess all symptoms. Circle the number from 0-10 according to how you would rate your symptoms. 0= no symptoms, 10= most severe symptoms.										Most severe symptoms
HEADACHE	0	1	2	3	4	5	6	7	8	9	10	
GENERAL ACHES/PAINS	0	1	2	3	4	5	6	7	8	9	10	
FATIGUE	0	1	2	3	4	5	6	7	8	9	10	
WEAKNESS	0	1	2	3	4	5	6	7	8	9	10	
NASAL STUFFINESS	0	1	2	3	4	5	6	7	8	9	10	
NASAL DRAINAGE	0	1	2	3	4	5	6	7	8	9	10	
SORE THROAT	0	1	2	3	4	5	6	7	8	9	10	
COUGH	0	1	2	3	4	5	6	7	8	9	10	
HOARSENESS	0	1	2	3	4	5	6	7	8	9	10	
CHEST DISCOMFORT	0	1	2	3	4	5	6	7	8	9	10	
CHILLS	0	1	2	3	4	5	6	7	8	9	10	
FEVER	_____ °F											
OTHER SYMPTOMS (please list) _____	0	1	2	3	4	5	6	7	8	9	10	

ized diary (McDowell, 2006) provided by the research group. Blood samples, basic physical examination, vital signs (blood pressure, heart rate, temperature, and weight), medication, health summaries (including an on-site completed Short Form 36 [SF-36]) (Patel, Donegan, & Albert, 2007; Ware, & Sherbourne, 1992), and summarized diary information were performed and collected at each clinic visit.

The diagnosis of common cold or influenza-like symptoms was primarily based on the provided self-report diaries (see Figure 1). *Common cold* was clinically defined as an upper respiratory tract infection of viral etiology consisting of one or more of the following symptoms: cough, generalized malaise, headache, hoarseness, low-grade fever, nasal drainage, nasal stuffiness, and sore throat (Centers for Disease Control and Prevention, 2007).

Influenza-like symptoms were clinically defined as a respiratory

tract infection of viral etiology and acute onset, more severe than the common cold, and consisting of one or more of the following symptoms: chest discomfort, fever of 102 to 105 degrees Fahrenheit, myalgia, nonproductive cough, prominent headache, rhinitis, and sore throat (Centers for Disease Control and Prevention, 2007). Cold and flu-like symptoms could clinically overlap or occur simultaneously.

The incidence of cold or flu-like symptoms was defined as the number of clinical occurrences reported during the entire 12-week study period. *Duration of symptoms* was defined as the number of consecutive illness days, and severity was also recorded on a scale from 0 to 10 as described by the diary.

Adverse events (AE) were defined as any clinically unfavorable and unintended sign or laboratory finding, symptom, or new or exacerbated disease correlated with the utilization of the interventional supplement or

placebo. A *serious adverse event (SAE)* was defined as any medical occurrence that included at least one of the following conditions: life-threatening, requiring hospitalization, or resulting in disability, incapacity, or death during the time of the entire 12-week trial period. Study medical staff analyzed each participant's past and current health and illness history to determine if any incident or prevalent AE was attributed to a pre-existing condition or a current illness unrelated or associated to the study medications. An overview of the diversity of the symptoms provided in this diary to evaluate cold and flu symptoms is provided in Figure 1.

Results

EpiCor significantly reduced the incidence and duration of the common cold or flu-like symptoms compared to placebo. Incidence was significantly ($p = 0.011$) reduced from a mean of 1.42 (95% CI 1.32 to 15.3) to 1.26

(95% CI 1.18 to 1.33) clinical occurrences, and this result remained significant regardless of baseline status, including age ($p = 0.54$) or gender ($p = 0.94$). Duration was also significantly ($p = 0.028$) reduced from 5.01 to 4.16 symptom days (95% CI 3.66 to 4.66) compared to a placebo mean of 5.01 with placebo (95% CI 4.40 to 5.62), and this result also remained significant regardless of baseline status including age ($p = 0.63$) or gender ($p = 0.34$). Severity increased significantly ($p = 0.002$) from 3.17 (95% CI 2.98 to 3.37) to 3.84 (95% CI 3.58 to 4.11). EpiCor in particular had a significantly greater reducing impact on several specific symptoms compared to placebo, including incidence of hoarseness ($p = 0.008$), incidence of nasal stuffiness ($p = 0.008$), and duration in weakness ($p = 0.008$).

No abnormalities were found with any of the laboratory serologic parameters when comparing EpiCor at baseline to EpiCor at 12 weeks, or when comparing EpiCor to placebo.

The rate of reporting AEs was 30.8% for EpiCor and 39.1% for the placebo group, which is a non-significant difference ($p = 0.232$). No serious AEs were reported for subjects receiving the interventional dietary supplement. However, two serious AEs were reported in the placebo group: one hospitalization for pneumonia and one hospitalization for bowel obstruction in a subject with a past history of this condition. Both subjects recovered without incident and both were withdrawn from the study upon the advice of their primary care physicians.

Discussion

The results of this, the largest randomized trial of a modified yeast-based product, at least initially espouses the previous observations and data surrounding the background information on this *Saccharomyces cerevisiae* product. Both incidence and duration of cold and flu-like symptoms were significantly reduced, including almost a full day of duration reduction when harbor-

ing cold and flu-like symptoms. The accuracy and pertinence of these significant clinical findings are further enhanced when the 95% CIs were evaluated because of the narrow range in the mean of each of these findings. However, the small but significant difference in severity seemed less clinically relevant because this clinical feature is more difficult to capture based on the inherent subjectivity of severity as an endpoint in a variety of infectious diseases (Ioachimescu, Ioachimescu, & Iannini, 2004).

Strengths

The strengths of this study, especially for a dietary supplement, are not only numerous but impressive. The large number of participants, randomization of group assignment, maintenance of the double-blind, and the use of placebo as a control are features that set a novel standard, which is not commonly observed in over-the-counter product studies. In addition, the strict exclusion and inclusion criteria, and the real-world setting of utilizing a product in an adjuvant setting further establish the integrity of the observations. Finally, the enormous financial cost (approximately a quarter of a million dollars) to conduct such a clinically robust trial is further testimony to the investigative team and the manufacturer of this product and hopefully continues to establish a new paradigm in the dietary supplement industry.

Limitations

The limitations of this study should also be emphasized. More frequent clinical visits, albeit costly, would have allowed for closer follow up and more precise serologic observations. The standardized diary is an imperfect system of measure but was reviewed with each visit. Additional immunologic plasma, serum, urine, and imaging studies could have further enhanced the accuracy of the trial, including the duration and severity data. However, it should be reiterated that the monitoring of primary symptoms in the case of

colds and flu-like symptoms remains the gold standard for primary outcome measures utilized in conventional medical prescription drug and vaccine trials (Eccles, 2005). Thus, the research team subsequently decided to mimic these outcome measurements to not only determine conventional effectiveness but also to further enhance the integrity of this study.

Conclusion

EpiCor, a modified yeast-based (*Saccharomyces cerevisiae*) dietary supplement taken daily, appears to significantly reduce the incidence and duration of cold and flu-like symptoms when compared to placebo in subjects vaccinated for seasonal influenza. This is also the largest randomized placebo-controlled trial to date to demonstrate that a yeast-based product, acting as an adjuvant intervention to a conventional therapy, may improve immune surveillance and outcomes in an otherwise healthy population. An additional trial of EpiCor alone compared to placebo, regardless of vaccine status, has also been initiated due to the promising outcomes with this over-the-counter intervention. ■

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Additional Readings

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