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CITRUS AURANTIUM AS A THERMOGENIC, WEIGHT-REDUCTION REPLACEMENT FOR EPHEDRA: AN OVERVIEW

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Abbreviations: BMI = Body Mass Index, BMR = Base Metabolic Rate, RMR = Resting Metabolic Rate, SBP = Systolic Blood Pressure.

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Abstract

Obesity is a serious health problem throughout the world. More than half of U.S. adults are overweight (61%) and more than a quarter (26%) of U.S. adults are obese. The inability of many individuals to keep their weight in check by diet and exercise has created a need for additional therapeutic means to combat obesity. Despite great effort, the pharmaceutical industry has not come up with the solution; because most weight-loss drugs to date have serious adverse effects to health and well-being. The theory that beta agonists, especially beta 3 agonists, can affect body weight and fat mass is well accepted. Ephedrine has proven time and time again that it is an effective weight loss agent through its ability to increase thermogenesis and quench appetite. However, the publicity concerning adverse reactions has led to its gradual withdrawal from use by many despite the perceived consequences of obesity. Many companies are now substituting *Citrus aurantium* for ephedra in their formulations. *Citrus aurantium*, an agent containing beta agonists, has been reported to aid in weight loss in two studies and increase thermogenesis, at least to some extent, in three studies. Colker *et al.* (1999) reported that in a double-blind, placebo-controlled, randomized study the subjects receiving a combination of *Citrus aurantium*, caffeine and St John's Wort, lost significant amounts of total body weight while on a strict diet and exercise. Those in the placebo and control groups who also were on the same restricted diet did not. However, intergroup analysis showed no statistical significance among the weight changes in the three groups. In contrast, the loss of fat mass in the test group was significantly greater compared to the placebo and control groups. Jones describes an open labeled study performed on 9 women. The subjects showed a mean of 0.94 kg lost during the first week when no product was given and 2.40 kg during the second week when a *Citrus aurantium* product was taken. Body weight losses were statistically greater during the second week compared to the first week. Since most clinicians would agree that the most weight loss should occur initially coinciding with a greater fluid loss during the first week, these differences are even more remarkable. Three studies reported increased metabolic rates when ingesting *Citrus aurantium* products, however, at least two of these studies were acute. At present, *Citrus aurantium* may be the best thermogenic substitute for ephedra. However, more studies are needed to establish this definitively.

Importance of Weight Control

Obesity, even the overweight state, is a significant health problem that is estimated by certain criteria to affect approximately one-third of all Americans (PHS 88-50210; NIH Consensus Statement 1985). It is believed that obesity and its complications are responsible for nearly 300,000 deaths each year via an association with serious chronic disorders (Manson *et al.*, 1995; McGinnis and Foege, 1993; Pi-Sunyer, 1991, 1993; Sjostrom 1992). Being overweight is also a common problem throughout other areas of the industrialized world. The World Health Organization (WHO) recently reported on the global development of obesity and established a task force to consider how this virtual epidemic could be kept in check (PHS 90-50212). According to WHO there are over 300 million obese adults. So far, it has been a losing effort. Even though many individuals spend billions of dollars on weight loss aids, 90-95 % of those individuals who lose weight subsequently regain it (WHO 1997; Colditz, 1992).

While there is a universal desire to "look good", there are other, perhaps better, reasons to maintain an optimal body weight as indicated above. Many "life-threatening" disorders including higher rates of heart disease, diabetes, cancer, arthritis, and shorter life span are associated with the overweight state and its consequences (Anderson-Parrado, 1999; Preuss HG, 1997; Preuss *et al.*, 2001). Obesity is the second leading cause of premature death in the U.S.A. Three hundred thousand Americans die each year from complications caused by obesity. Obesity can also limit physical mobility, which may decrease a person's freedom and independence. Over the years, an exceedingly strong association has been made between the overweight state, especially abdominal obesity, and cardiac tragedies such as atherosclerosis, myocardial infarctions and strokes (Markus *et al.*, 1997; Yamamoto *et al.*, 1997). The complications of obesity can be placed at the top of the list along with smoking, hypertension, and dyslipidemias as a major risk factor for these unhealthy conditions. It is not entirely by chance that the incidence of diabetes is increasing in a manner similar to obesity, because there appears to be a connection between youth-onset type II diabetes and obesity (Preuss *et al.*, 2001; Scott *et al.*, 1997). In a study conducted by the American Cancer Society, 750,000 individuals were surveyed over a 13-year period (Monson, 1996). "After accounting for the effects of age and cigarette smoking, people whose body weight was 40% higher than average had an overall increased risk of cancer death – 33% increase in

men (colorectal and prostate) and a 55% increase in women (gallbladder, breast, cervix, endometrial, uterus, and ovarian)." Middle age and older women who lose as little as 10 pounds over a 10-year period decrease their chances for development of osteoarthritis in the knees (Anderson-Parrado, 1999). It has long been accepted from studies on rodents and primates that caloric restriction may lead to lower body weight, enhanced insulin sensitivity, and lessen most of the cardiovascular risk factors resulting in the possibility of a longer life span in humans similar to that found in animals (Preuss *et al.*, 2001; Weindruch and Sohal, 1997).

General Considerations in the Treatment of the Overweight State

Although it is generally accepted that overweight and obesity are associated with several, severe health perturbations, there is less agreement concerning treatment (WHO, 1997). Some even argue against any treatment because of the difficulty in maintaining long-term weight loss. Far too many have experienced the "yo-yo effect", i.e., those involved in weight loss regimens experience multiple periods of successful weight loss followed eventually by periods of weight regain. Thus, an individual may go through many cycles of weight gain, weight loss, and weight regain in a lifetime. Unfortunately, negative consequences could result from repeated weight cycling (WHO, 1997). While a low caloric diet and exercise remain the cornerstones of therapy, many people cannot carry out these procedures adequately and require safe means to help with the initial weight loss and/or maintenance of a near ideal weight. At the moment, it is widely accepted that the public needs some aid to prevent and/or overcome obesity and maintain a reasonable body weight without experiencing the "yo-yo effect."

Pharmaceutical Approaches to Weight Loss

The pharmaceutical industry has attempted to meet the public need for weight loss assistance, but the serious, irreversible adverse side effects associated with some weight-management drugs have compromised their usefulness (Volmar and Hutchins, 2001; Cheng, 2000). Currently, adverse reactions derived from Meridia (Sibutramine) and Orlistat (Xenical), two marketed pharmaceuticals, are being reported in the media. The former has been associated with cardiovascular problems, constipation, dry mouth, headache and insomnia and the latter with explosive, difficult-to-control diarrhea and anal oil leakage, fatty or oily stool, fecal urgency and frequent bowel movement. The

cardiovascular problem relating to the use of Meridia leads to high blood pressure and an increase in heart rate. Also, once the individual quits taking the medicine, blood pressure and heart rate return to the normal. Recently, USA Today ran a front-page story describing the extent that the pharmaceutical industry is going to in order to develop effective anti-obesity medications (USA Today, April 29, 2002, Life SX 1D-2D). Because of serious side effects emanating from the use of pharmaceuticals, many medicinal plants (natural supplements) have been considered as therapy for overweight-obesity (Volmar and Hutchins, 2001).

Natural Products to Enhance Weight Loss via Enhanced Thermogenesis

An important means to enhance weight loss is to increase calorie utilization, i.e., increase metabolism. The mass of the body depends upon the balance of calories taken in and those consumed. Obviously, weight-losing diets stress caloric restriction, and an increase in exercise regimen. Accordingly, the body's ability to burn calories is important in the overall balance, i.e., whether the individual loses weight, gains weight, or remains the same. Focusing on caloric consumption, the contribution of reduced energy expenditure to the development of obesity has been a point of controversy. Ravussin *et al.*, (1988) concluded from data they gathered that a low rate of energy expenditure might contribute to the aggregation of obesity in families. Accordingly the ability of a dietary supplement to enhance thermogenesis and metabolism would be important in the therapeutic regimens to treat overweight-obesity. This has been proven time and again with the use of ephedra alkaloids like ephedrine (Astrup *et al.*, 1986, 1990, 1992, 1993). The latter as a supplement is derived largely from the plant Ma Huang and is especially effective when coupled with caffeine (Astrup, *et al.*, 1990).

The safety of ephedra-use for weight loss has come under attack over the last few years. Although many controlled clinical trials have failed to associate proper use of ephedra with serious adverse reactions, papers published in the New England Journal of Medicine (Haller and Benowitz, 2000) and the Mayo Clinic Proceedings (Samenuk *et al.*, 2002) used information supplied by the FDA to indicate the possibility that uncontrolled ephedra usage is dangerous.

Ephedra: An Overview

Ephedra contains the alkaloid ephedrine that is commonly used in over-the-counter products designed to relieve bronchitis, nasal

congestion and asthma. (Chen and Schmidt, 1930). In addition, it induces thermogenesis by increasing cellular utilization of energy in cells of adipose tissue and skeletal muscle (Chen and Schmidt, 1930). One study reported that dieting women given 20 mg of ephedrine lost twice as much fat (an additional 9.9 pounds) and lost three quarters less muscle (6.2 pounds) than the placebo group (Astrup *et al.*, 1992). In a head to head comparison, ephedra plus caffeine proved superior as a weight loser than dexfenfluramine (Astrup *et al.*, 1992). Ephedrine has both thermogenic and appetite-suppressing effects. A very important consideration for dieters is that ephedrine, caffeine, and aspirin can prevent the compensatory decline in metabolism accompanying dieting (*Dulloo and Miller, 1986*). Even though the stimulatory effects on the cardiovascular system of ephedrine have been reported to eventually disappear due to the development of tolerance, the thermogenic properties continue to be enhanced (Chen and Schmidt, 1930).

The safety of ephedra as an over-the counter remedy has come under persistent attack despite a thorough examination of the issue in the Cantox Report (2000). The mass of data accumulated in the Cantox Report suggests that the agent is safe and effective when used daily in a split dosage -- divided into three parts with no dose to exceed 30 mg. Further studies are necessary to determine whether these recommendations can be carried out for more than six months (Cantox Report 2000). *In vivo* studies in rabbits demonstrate that small doses could be given indefinitely by any route without creating toxicity (Chen, 1926). Hobbs (1926) reported that the agent has been available in Germany since 1896 and in the US since 1926. He states, "there are an estimated 55 million people who are obese in the US with 300,000 of them dying every year from obesity-related causes. If ephedrine helps even a tiny fraction of the obese population lose weight, it is likely to save hundreds of thousands of lives every year." According to Hobbs (1926), the herb Ma Huang has been used in Chinese medicine for more than 5,200 years. A large Government funded study reported that large doses of ephedrine did not change the life span of mice or rats with the exception of female rats where the life span was significantly increased (Chen, 1926).

Despite the evidence gathered in the Cantox report and multiple other investigations reporting safety (Cantox Report 2000; Daly *et al.*, 1993), other groups have written about adverse reports gathered by the FDA (Haller and Benowitz, 2000; Samenuk *et al.*, 2002). Many people

in the nutritional world believe the majority of the adverse case reports gathered by the FDA should not cause removal of ephedrine from the shelves for a number of reasons: (1) The directions for taking ephedrine exclude hypertensives and patients with cardiac arrhythmias. Many of the reports of adversities include a large number of these individuals. (2) Many further believe a significant portion of severe adverse reactions gathered over the years are due to coincidence, i.e., many people with cardiovascular disorders and many taking ephedra lead to the probability that expected adverse events in the former will be linked up with ephedra-taking rather than the expected outcome from the disease itself. (3) Some consumers are knowingly over-dosing figuring that increasing the dose will cause even more dramatic effects in weight loss over a shorter duration of time. Hobbs provides evidence that more people die from bike accidents, ibuprofen over-dosing, and contaminated hamburgers than from taking ephedrine (Hobbs, 1926). Considering all the facts and reports, the regulatory agencies have called for further studies on the matter. However, many lawyers chose to accept the reports suggesting potential toxicity as clearly proven and call for the public via media and the Internet to bring cases seeking huge monetary compensations against manufacturers of ephedrine products. Thus, the availability of this weight loss agent is disappearing to a great extent, because of the desire to avoid lawsuits and the rising cost of insurance.

Role of Caffeine in Weight Management

Caffeine is often added to formulas containing ephedra alkaloids. Caffeine, a methylxanthine, often enhances the thermogenic properties of other agents possibly through an action on phosphodiesterases. However, many studies suggest that caffeine on its own has intrinsic weight-losing and thermogenic properties, in at least some individuals. Dulloo *et al.*, (1989) found that 100 mg caffeine increased the resting metabolic rate of both lean and post-obese human volunteers by 3-4% ($p<0.02$) over 150 min and improved the defective diet-induced thermogenesis observed in post obese volunteers. These benefits have also been demonstrated by Yoshida *et al.*, (1994) and Bracco *et al.*, (1995).

Beta Sympathomimetic Agents and Weight Loss

What is a suitable substitute for ephedra? How about another beta agonist? The sympathetic nervous system is involved in the regulation of energy. Therefore, pharmacological manipulation of the

system offers a mechanism of targeting a reduction in excessive body fat stores. Many beta-adrenergic agonists are known to increase muscle mass while concurrently decreasing fat mass (Yang and McElligott, 1989; Astrup, 1986). Prolonged treatment with sympathomimetic compounds reduces energy intake and increases energy expenditure (Yang and McElligott, 1989), and reduced sympathetic nervous activity is associated with body weight gain (Spraul *et al.,* 1993). Among antagonists of the sympathetic nervous system, only beta blocking drugs were able to antagonize the adrenergic lipid mobilization specifically (Wenke *et al.,* 1967). The latter finding supports the hypothesis that beta agonists would be helpful in a weight reduction program.

As a general principle, alpha activation by adrenergics causes contraction of smooth muscle (except for intestinal smooth muscle), while beta activation causes relaxation of smooth muscle and stimulation of the myocardium. The fact that alpha- and beta- receptors are further broken down into subtypes -- beta 1, beta 2, and beta 3 types further complicate this scenario. The beta 3 receptor appears to be responsible for the lipolytic and thermogenic effects of adrenergic agents, while interaction of the other two types control cardiac effects (Yang and McElligott, 1989; Spraul *et al.,* 1993). Accordingly, the ideal fat losing agent would have a preponderance of beta 3 effects, with much less influence than ephedra over the beta 1 and 2 receptors. It is believed that the alkaloids in *Citrus aurantium* simulate this condition, at least to some extent. In addition, the ephedra alkaloids of *Citrus aurantium* supposedly enter the central nervous system to a much lesser extent than the ones in ephedra (Jones, 1999). Accordingly, *Citrus aurantium* seems to have much less adverse effect via stimulation of beta 1 and 2 receptors than ephedrine (Jones, 1999; Kalman, 1999). The importance of the beta 3 receptor in the therapy of obesity is evident through the efforts of the pharmaceutical industry to develop drugs, which activate this receptor (Weyer *et al.,* 1999). Much has been written about the drug BRL 26830A, a relatively new beta adrenoceptor agonist that has been used to bring about weight loss (Connacher *et al.,* 1998; Arch and Ainsworth, 1983). BRL 26830A was developed specifically to be an agonist for beta 3 receptors, and its ability to cause significant weight loss adds credibility to the theory that stimulation of this receptor site would be important to achieve therapeutic weight loss (Landsberg and Young, 1993).

***Citrus aurantium*: An Introduction**

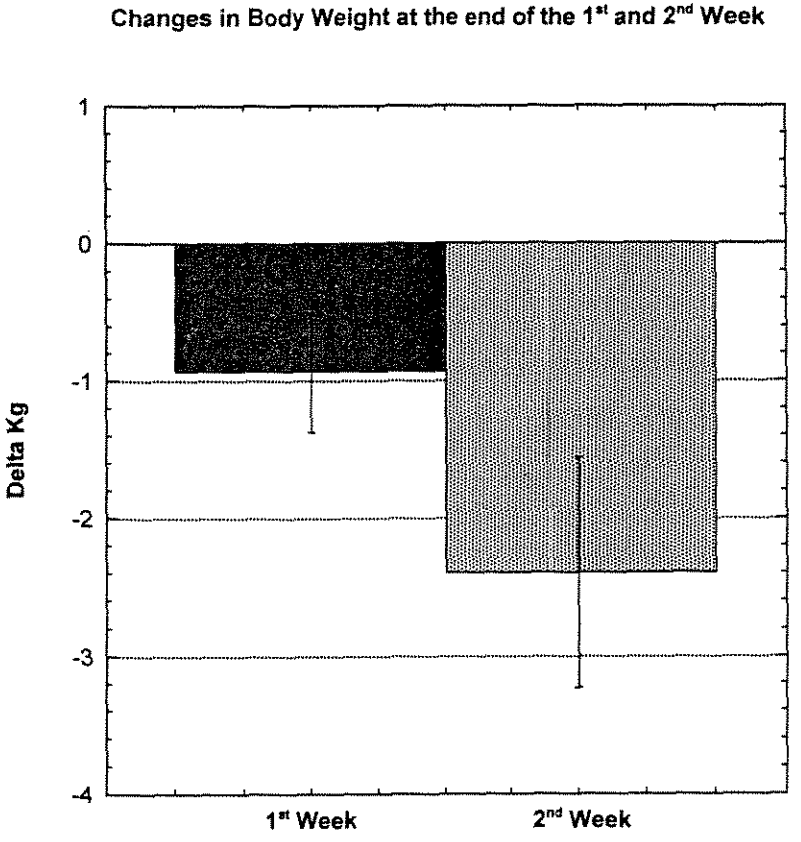
Citrus fruits and its constituents have long been associated with obesity treatment. The use of grapefruit ingestion in a weight loss program is familiar to most, although the scientific documentation of effect is somewhat lacking (Kalman, 1998; Weyer *et al.*, 1999). Nevertheless, consideration of *Citrus aurantium* (bitter orange) as an adjunct in a weight loss program is realistic. Active components are derived from inedible portions of immature fruits. Moro and Basile (2000) describe *Citrus aurantium* as a natural medicinal substance with a direct action to stimulate metabolism. "A medicinal plant that has recently enjoyed a surge of interest, especially in countries other than Italy, is the bitter *Citrus aurantium* whose active component is synephrine. This amine acts on the alpha and beta receptors by activating thermogenesis ...." *Citrus aurantium*, also known as bitter orange, contains small amounts of alkaloids and other components such as synephrine, octopamine, hordenine, m-methyltyramine, and tyramine. These are mainly adrenergic agents with beta-agonistic actions that stimulate lipolysis and increase resting metabolic rate. The theory behind the use of *Citrus aurantium* is that it will augment thermogenesis and calorie consumption, but at the same time, produce less cardiovascular perturbations than ephedrine (Arch and Ainsworth, 1983).

Citrus aurantium and Weight Management

Using intragroup analysis, Colker *et al.* (1999) reported that a test group receiving a daily dose of 975 mg of *Citrus aurantium*, 528 mg caffeine, and 900 mg of St John's Wort (n=9) lost body weight in contrast to a placebo (n=7) and a control group that received no pills (n=4) (Colker, 1999). The test group lost 1.4 kg of body weight over 6 weeks, which was significant ($p<0.05$). However, intergroup comparisons showed no statistically significant differences among the three groups. Similar to ephedra formulations (Astrup and Toubro, 1993; Astrup *et al.*, 1990), caffeine was added to enhance the thermogenic effects of *Citrus aurantium* (Astrup *et al.*, 1992; Daly *et al.*, 1993; Kalman, 1999). Noting that obesity is often associated with depression. St. John's Wort was included in the formulation. All groups were limited to an 1,800 kcal diet/day and performed a 3-day per week supervised exercise program.

The fat loss in the test group averaged even more - 3.1 kg, whereas the placebo group gained approximately 0.6 kg. The loss of fat

mass reported in the test group was significantly different from both the placebo and control groups whether calculated as fat mass (kg) or percent body fat (%) when analyzed by intergroup analysis. Fat mass was estimated by bioelectrical impedance technology that is commonly used today for such an assessment. The increase of basal metabolic rate (kcal/d) of 2-3% in the test group was also significantly increased when compared with the two other groups.



This contrasts with the placebo group that had a significant decrease in basal metabolic rate, characteristic of individuals undergoing caloric restriction. It was mentioned previously that the basal metabolic rate characteristically decreases in response to a low caloric regimen. However, the methodology to determine basal metabolic rate was not given in the paper. No serious adverse reactions were reported, i.e., no

significant changes in blood pressure, heart rate, electrocardiographic findings, serum chemistries, or urinalysis findings were noted in any of the groups. In conclusion, Colker *et al.* (1999) reported that in a double-blind, placebo-controlled, randomized study where patients receiving a combination of *Citrus aurantium,* St John's Wort, and Caffeine lost total body weight and fat mass in contrast to the other two control groups.

Jones (2001) performed an open labeled study on 9 women – where 6 were mildly obese, 1 moderately obese, and 2 slightly overweight. Their body mass index's (BMI) ranged from 23.1-33.4. Over the first week, their diets contained 900-1000 kcal per day, more than 100 g protein per day, and less than 100 g carbohydrate per day. From day 8 on, they were provided 325 mg dried *Citrus aurantium* extract, 125 mg of dried *Paullinia cupana* extract, 5 mg of *Ginkgo biloba* and 5 mg of Panax ginseng extract. They received 2-5 capsules per day. This corresponds to a daily intake of 27.0-67.5 mg of total alkaloids. Statistical analysis showed a mean of 0.94 kg of weight loss during the first week when no product was given to the nine subjects and 2.40 kg during the second week when product was taken (Fig. 1). Body weight losses were statistically greater during the second week compared to the first week. Since most clinicians would agree that the most weight loss should occur initially coinciding with a greater fluid loss during the first week, these differences are even more remarkable (Fig. 1).

Thermogenesis of Citrus aurantium Alone and in Combination

Colker *et al* (1999) reported a significant increase in basal metabolic rate (BMR) in the group taking the compound containing *Citrus aurantium*, although the method to ascertain this was not reported. Thus, the thermogenic formula containing *Citrus aurantium* prevented the decreased basal metabolic rate usually seen in dieters. The increases in metabolic rate in the test group were significantly increased compared to those changes in the placebo and control groups. Two reports (Pathak and Gougeon, 1999; Hedrei and Gougeon, 1997) were written by investigators working at McGill University, Canada. One study was performed on obese subjects (Pathak and Gougeon, 1999) and the other on normal weight subjects (Hedrei and Gougeon, 1997). In the study comprised of five healthy, but obese, females, resting metabolic rate (RMR) was measured over 20 minutes by indirect calorimetry. Three separate measurements were made:

1. Thermogenic effects of food alone
2. Effects of *Citrus aurantium* formula alone
3. Effects of food + *Citrus aurantium* formula

A significant increase in the metabolic rate over baseline was seen in the presence of food. The *Citrus aurantium* formula increased the metabolic rate even more over a three-hour interval after ingestion of food. The thermogenic response of the meal was significantly greater with the concurrent intake of *Citrus aurantium* formula (CAF) (18.3% meal + CAF compared with 13.8% meal alone, p=0.03). Epinephrine excretion increased significantly in response to *Citrus aurantium*, while norepinephrine and dopamine excretion did not. No significant changes in systolic blood pressure (SBP) or heart rate were reported.

Another similar but separate study on metabolic rates in 6 males and 1 female (normal weight) was carried out at McGill University (Hedrei and Gougeon, 1997). Five *Citrus aurantium* containing pills were taken. The *Citrus aurantium* formula elicited an increase in respiratory quotient (RQ) within the first 50 minutes after consumption. There was a 14.9 % increase above the resting energy expenditure when the capsules were added to the mixed meal. In response to the *Citrus aurantium* formula, urinary epinephrine and dopamine increased significantly, while norepinephrine did not. Furthermore, no irregular changes in pulse rate or blood pressure were reported.

Citrus aurantium appears to be a possible thermogenic substitute for ephedra based upon two studies showing enhanced weight loss compared to control (Colker *et al.,* 1999; Jones, 2001) and three studies reporting increased metabolic rates with its use (Colker *et al;.,* 1999; Pathak and Gougeon, 1999; Hedrei and Gougeon, 1997). More studies and widespread use of this natural product will reveal the veracity of the preceding statement as well as the relative safety of *Citrus aurantium* compared to ephedra. In addition to thermogenesis, this agent might work also via some appetite suppression like ephedra and via its effects on the insulin system. Furthermore, agents that overcome insulin resistance may also be beneficial in increasing metabolism and helping with fat loss in obese subjects without adverse side effects (Crawford *et al., 1999*; Krieger and Landsberg, *1988*; Preuss and Bagchi, *2002*; Preuss *et al.,* 2001; Seifert and Burke, 2002).

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