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REVIEW ON ROLE OF NUTRACEUTICALS IN STRESS MANAGEMENT

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ABSTRACT: Stress is a complicated process that affects everyone differently. When the body is exposed to stressors, it initiates a series of coordinated responses called "stress responses," which include behavioral changes, immunological regulation, hormone release, and various physiological changes. Stress is the physiological response to risk or pressure, and it displays physically as fatigue or energy loss and psychologically as irritation or tension. Chronic stress or despair, which are issues of unmet health care need, may develop if they remain untreated. Treatment and preventative strategies that are based on scientific evidence are required. Current medicines show a therapy gap. The majority of medications solely address psychological or physical stress symptoms. Furthermore, psychotropic medicines, which are occasionally given for stress, frequently have undesirable side effects and cause danger of overuse. Pharmacological therapy should provide advanced care for all stress symptoms while also having a favourable safety profile. One of the most effective techniques for dealing with stress is to eat stress-relieving and nutrient-reducing meals. The term "nutraceutical" is composed up of the words "Nutrient" and "Pharmaceuticals" for dealing with stress is to eat stress-relieving and nutrient-reducing meals. Nutraceuticals are products that can be used for both nutrition and therapy. Nutraceuticals include foods such as dietary fibre, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants, and other herbal/natural foods. These nutraceuticals play a distinct and important role in stress management. This review aims to find out how nutrients and diets influence stress management.

INTRODUCTION: Hans Selye, a Canadian endocrinologist, introduced the term stress in healthcare in 1949. The body's reaction to a novel environment, as well as its stereotyped, non-specific response to external cues that disrupt an individual's balance, is referred to as stress (Selye-1956).

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A stressor is an individual or circumstances that cause a person to respond to stress. A stressor is a biological or chemical substance, environment conditions, external stimulation, or event that causes the person to be more stressed [1].

Stress refers to the body's adaptation to a new circumstance as well as its stereotyped and non-specific response to external stimuli that disrupt the personal balance. It's also a psychological approach to stress management and regulation that comprises understanding and preparing the body for varying conditions. Stress is a healthy and natural reaction to a risky situation. Increased anxiety and stress reports have forced us to seek medical and non-

medical remedies in order to live a stress-free existence [2]. The stress response is a well-developed physiological and neurological phenomenon that regulates the interaction of environmental, chemical and psychological elements. Such responses are critical to a person's survival in a stressful situation. The manner people respond to stress varies from person to person. Genetic factors, past life episodes, behaviour and socioeconomic conditions influence how we react to stress. Stress causes the brain to release stress hormones, which trigger the fight-or-flight response, strengthening the immune system. It is likely to experience both short-term and long-term stress. Acute stress has reversible physiological changes. Acute stress can be managed effectively and at the right time, and homeostasis can be achieved quickly. Chronic stress, on the other hand, can cause serious health problems like metabolic syndromes, obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), severe heart issues, diabetes and high blood pressure, poor memory and intelligence, gastrointestinal problems, tiredness syndrome, autoimmune disorders, and endocrine disorders [3, 4].

A substance that seems to have pharmacological significance or offers protection against chronic illness is called a nutraceutical product. Nutraceuticals can be used to maintain a healthy lifestyle, slow down the aging process, boost the immune system, improve survival and maintain the body's structure and function. Nutraceuticals include dietary fiber, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants, and other herbal/natural foods. These nutraceuticals play a distinct and important role in stress management. This review aims to find out how nutrients and diets influence stress management.

1. Neurobiology of Stress:

1.1 Hormonal Involvement: A nutraceutical product is a chemical that appears to have pharmacological value or provides protection against chronic disease. Nutraceuticals can help people live a healthier lifestyle, slow down the aging process, boost your immune system, increase your chances of survival and keep your body's structure and function in good shape. Nutraceuticals include dietary fibre, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants, and other herbal/natural foods. These nutraceuticals play a distinct and important role in stress management. This review aims to see how food and nutrition affect stress management [5]. The HPA axis activation is promoted by stress-induced norepinephrine (NE) release in particular brain locations (such as the hippocampus and amygdala). Any imbalance in these systems will result in several stress-related problems. The anterior pituitary glands' primary stimulator for ACTH production is CRF. The release of glucocorticoids into the systemic circulation is triggered by activation of this axis (also known as the HPA axis). As a result, glucocorticoids are believed to play an important role in the organism's stress response. The cognitive function of humans and animal models is affected differently by stress and glucocorticoids. Stressful experiences and adrenal hormones can create short-term and reversible impairments in situational and spatial memory in both animal and human models. Stress has acute effects that last from a few hours to a day and are typically reversible and selective for certain tasks or situations [6, 7, 8].

1. 2 Neurotransmitters and Stress:

1.3 Gamma-aminobutyric Acid (GABA): It's a key inhibitory neurotransmitter in the central nervous system. It is generally known that GABA and benzodiazepine receptors have a role in stress disorders (such as anxiety, epilepsy, sleeplessness, and seizures). Stress has been shown to alter the content of GABA neurotransmission, suggesting that GABA is implicated in stress-related behavioural and physiological changes. Melatonin is a hormone produced in the pineal gland and released into the circulation and cerebral fluid. According to the study, melatonin's hypnotic effect is mediated by GABAergic pathways. The amygdala and hypothalamus produce CRF and GABA in response to stress [9, 10].

1.4 Dopamine (DA): Dopamine is a neurotransmitter that regulates the neuronal transmission and circuit functioning. Physically and psychologically, stresses stimulate dopaminergic pathways in the brain, resulting in short- and long-term alterations in neuronal function. Through regulation of other chemical transmitters, Dopamine systems contribute to the production of the stress response and mitigate stress responses [11].

1.5 Norepinephrine: The stress hormone corticotropin-releasing factor (CRF) appears to have a significant role in regulating the central norepinephrine (NE) system. Depression may have an impact on immune system responses. Increased macrophage activity accelerates NE turnover in the hypothalamus, resulting in increased CRF release and activation of the hypothalamic-pituitary-adrenal axis, which produces glucocorticoids [12].

1.6 Serotonin: Both serotonin and stress have also been related to various psychological disorders. Stress affects several aspects of serotonergic signalling in the brain, and serotonergic drugs can assist in alleviating the consequences of stress. The effects of stress on the serotonin system are complicated, vary by area of the brain, and are dependent on the kind of stress, serotonergic marker, individual variability in adaptability, and genetic history [13].

1.7 Melatonin: Stress can impair pineal sympathetic inputs, leading to inconsistent melatonin synthesis and environmental maladaptation. Glucocorticoid disruption affects the pineal gland under stressful settings. Melatonin is a unique approach to the physiological treatment of stress and stress-related diseases. It is a short-acting hormone with low side effects that is rapidly degraded and eliminated by the body. Melatonin might potentially be utilized to improve the efficacy of primary immunizations (vaccinations) against antigens of all types that don't elicit a significant or long-lasting secondary (memory) response [14].

1.8 Glutamate: According to studies, glutamatergic innervations to the paraventricular nucleus (PVN) come from a wide range of brain locations, including the PVN and many other nuclei in and beyond the hypothalamus. The dorsomedial hypothalamic nucleus is a possible locus for glutamatergic neurons triggered by immobilisation stress among the neuroanatomical areas of glutamatergic afferents to the PVN [7].

2. Nutraceutical in Stress Management: Nutraceuticals and functional foods have recently gained a lot of interest due to their known safety and nutritional and therapeutic effects. Nutraceuticals include dietary supplements, value-added processed foods, and non-dietary supplements such as tablets, soft gels, and capsules containing bioactive ingredients. Nutraceuticals are defined as foods or dietary components that prevent and treat disease. These contain protein, vitamins, minerals, and compounds from natural sources. As Nutraceuticals contain phytochemicals, these are useful to delay, prevent and treat chronic inflammatory diseases [15, 16].

Spices and natural items have been used to treat numerous ailments since ancient times, with astonishing results. Advances in science and technology have led to the research and use of many phytochemicals with therapeutic properties from plant and non-plant sources.

The advancement in science and technology has led to the investigation and utilization of several phytochemicals with therapeutic properties from plant and non-plant sources, leading to a renaissance in the research of nutrition and human health, thereby creating opportunities for the advancement of novel dietary substances, leads to a renaissance in research on nutrition and human health, thereby creating opportunities for the development of new foods.

In the year 1989, the term nutraceutical was coined by Dr. Stephen De Felice, which comes from the combination of ‘nutrition’ and ‘pharmaceutical’. He defines a nutraceutical as "any substance that is a food or a component of food that delivers medical or health advantages, including illness prevention and treatment [17].

Nutraceuticals consist of isolated nutrients, dietary supplements and specific diets to genetically engineered designer foods and herbal products.

2.1 Nutraceuticals: Nutraceuticals or functional foods can be classified according to their natural sources, pharmacological conditions, or the chemical composition of the products.

1. It can be classified as goods derived from plants, animals, minerals, or microbiological sources based on their natural origins.

2. Chemical groups categorize nutraceuticals.

3. Nutrients are substances that have been proven to have nutritional activities, such as vitamins, minerals, amino acids, and fatty acids.

4. Herbs or botanical products as concentrates or extracts–Herbals.

5. Reagents derived from other sources (e.g., pyruvate, chondrotin sulfate, steroid hormone precursors) serving specific functions, such as sports nutrition, weight-loss supplements, conventional fortified foods, and meal replacements–Dietary supplements [17].

Even though there are a variety of medications available to treat stress, nutraceuticals are being investigated as stress management options. Nutraceuticals are foods or components that have medicinal or health benefits, such as disease prevention and/or treatment. Nutraceuticals have an advantage over the medicine because they avoid side effects, have naturally dietary supplements, *etc*. Based on their natural source, chemical grouping, Nutraceuticals are categorized into three key terms -nutrients, herbals, dietary supplements, dietary fiber, etc. Adaptogens are nutraceuticals that aid in the battle against physical stress. Adaptogens are natural substances that increase the ability of an organism to adapt to environmental factors and avoid damage from such factors; they cause a non-specific increase in the resistance of an organism to noxious influences. They must be non-toxic and almost free of side effects. They regulate and balance hypo and hyper stress, improve overall mental, physical, and emotional performance, and promote stress recovery [17]. Some of the stress-relieving nutraceuticals are discussed in this article.

2.2 Different Neutraceuticals used in Stress Management:

2.3 Siberian Ginseng: Tetracyclic triterpenoid saponins are active compounds. It has been shown to reduce the harmful effects of stress by maintaining vitamin C and reducing adrenal hypertrophy; nevertheless, it should be taken with caution because it might raise testosterone levels, perhaps leading to increased aggression. Siberian ginseng also has an anticoagulant action, which helps control blood sugar levels, another crucial aspect of stress management. Palpitations, sleeplessness, and hypertension are all possible side effects. According to preliminary research, Siberian ginseng may assist middle-aged people in improving their memory and sense of well-being. In addition, a combination of rhodiola, schisandra, and Siberian ginseng appears to increase attention, mental quickness, and accuracy in women who are stressed [18].

2.4 *Rhodiola rosea* (R. rosea): Rosavin is an active ingredient that plays an important role in reducing stress. It has been proven that the administration of Rhodiola improves attention, cognitive function, and mental performance in fatigue and in chronic fatigue syndrome supports immune function and increases exam performance.

Extracts of *Rhodiola rosea* operate as an adaptogen, providing generic tolerance to physical, chemical, and biological stressors. The stress-protective effects of *Rhodiola rosea* extracts have been found to be involved with the hypothalamic-pituitary-adrenal (HPA) axis. *Rhodiola rosea* extracts have also shown the stress-protective effects on different key mediators of stress responses, such as heat shock proteins (HSP), stress-activated c-JUN N-terminal protein kinase 1 (JNK1), Forkhead box O (FOXO) transcription factor DAF-1, cortisol, nitric oxide, and beta-endorphine. *Rhodiola rosea* extracts were shown to lower blood levels of corticotropin-releasing hormone and corticosterone via down-regulating the expression of c-FOS in the hypothalamus of stressed rats, according to Xia *et al* [19, 20].

2.5 *Schisandra chinensis*: Schisandra Berry / Magnolia Berry: Schizandra improves physical performance and reduces stress in the central nervous, sympathetic, endocrine, immunological, pulmonary, cardiovascular, and gastrointestinal systems. Schizandra has also been demonstrated to be helpful in the treatment of Alzheimer's disease. Amyloid-beta peptides are one of the components that contribute to the production of amyloid plaque, a substance seen in the brains of Alzheimer's sufferers. Schisandrin B prevents the brain from producing too many amyloid-beta peptides [21].

Fruits of *S. chinensis* can be used to alleviate insomnia. Schisandrin, the main component in *S. chinensis* fruit extract, possesses sedative and

hypnotic characteristics, which may be connected to serotonergic system regulation [22].

2.6 *Glycyrrhiza glabra* (Liquorice): GABAA receptors are a target for anaesthetics, neuroleptics, anxiolytics and anticonvulsant drugs [23]. GABA is the primary inhibitory neurotransmitter in the central nervous system. *G. glabra* can generate tranquil and anxiolytic effects by modulating GABAA receptors [24].

Glabridin had a sedative and hypnotic effects primarily potentiating GABA-induced responses through positive regulation of GABAA receptors. Glabridin may be used to treat Alzheimer's disease and dementia, among other neurodegenerative illnesses. Glabridin inhibited the depolymerization of the transthyretin dimer, according to simulated data from molecular dynamics and guided molecular dynamics. Glabridin is likely to be utilized to treat Alzheimer's disease since one of the key roles of transthyretin is to serve as a neuroprotective agent. Glabridin inhibits the absorption of 5-hydroxytrptamine by recombinant human serotonin transporter cells, suggesting that it potentially has anti-depressant properties [25].

The antidepressant action of liquorice (G. Glabra) aqueous extract appears to be mediated by an increase in norepinephrine and dopamine in the brain. Liquorice contains protein, amino acids, polysaccharides and simple sugars, mineral salts (calcium, phosphorus, sodium, potassium, iron, magnesium, silicon, selenium, manganese, zinc, and copper), pectins, resins, starches, sterols and gums. Oestrogens, tannins, phytosterols (sitosterol and stigmasterol), coumarins, vitamins (B1, B2, B3, B5, E, and C), triterpenes, saponins (the sweet flavour of the plant), flavonoids and glycosides have all been found. The saponins in liquorice are in the form of glucuronides, whereas the aglycones are in the form of oleananes [26, 27, 28].

3. Fish Oils: The diet can provide three different forms of omega-3s. DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) are two of them, and they're both found in fish oil (eicosapentaenoic acid). Omega-3 fatty acids are required for the healthy functioning of the human brain. If the body isn't getting enough EPA and DHA, depression might develop. The research is targeted into the potential advantages of omega-3 and fish oil in treating depression [29].

3.1 Ashwagandha (*Withania somnifera*): Due to presence of steroidal withanolides present in the root of the ashwagandha plant, it exhibits immunomodulatory, anti-inflammatory, and most importantly, adaptogenic properties. This plant provides potent nutritional support to both the mind and the body, mitigating the harmful effects of stress and promoting appropriate adrenal function. Ashwagandha has been shown to help minimise stress-related damage by boosting healthy brain function and regulating energy and mood. It lowers the level of a stress hormone, cortisol [30].

Withanine is the most common steroidal alkaloid that improves memory and cognition. It has a strong antioxidant activity and can help with oxidative stress-related neurodegeneration. The methanolic extract of ashwagandha root improves memory and inhibits the enzyme acetylcholinesterase, which is significant in neurodegeneration because it indirectly boosts cholinergic neuron transmission and is widely used to treat and control Alzheimer's disease In addition to antioxidant activity, the levels of catecholamines, such as serotonin, are increased by maintaining the levels of antioxidant enzymes, namely glutathione and catalase. Withanine inhibits nitric oxide activation, which helps to reverse oxidative stress and has significant neuroprotective properties. Somniferine, a neuroprotective and memory-enhancing compound derived from ashwagandha, is also widely used [31].

3.2 Holy basil: *Ocimum sanctum:* Holy Basil is a well-known adaptogen that is useful to treat anxiety, depression and stress management. It is, elevating the mood, relaxing the nervous system, the best stress reliever and effectively providing the body all the nutrients it requires to be healthy. It exhibits extremely little or no adverse effects [32].

3.3 Gotu kola (*Centella Asiatica*): This valuable plant increases mental clarity, concentration, and memory. Gotu Kola promotes a calm, harmonious mind and deep relaxation and cognition. One of the active compounds discovered in the herb's leaves, Asiaticoside, is thought to be responsible for the herb's medicinal properties.

Centella can block the phospholipase A2 group of enzymes, which have aberrant activity in the central nervous system in several neuropsychiatric illnesses, according to a research done on rats [33].

3.4 Turmeric (*Curcuma longa*): Curcumin has been shown to protect against Alzheimer's disease, tardive dyskinesia, severe depression, epilepsy and other neurodegenerative and neuropsychiatric conditions. It is thought to work primarily through anti-inflammatory and antioxidant effects. It's also a powerful inhibitor of reactive astrocyte expression, which keeps cells from dying. Curcumin also affects the amounts of neurotransmitters in the brain. Although turmeric and curcumin are typically safe to consume, therapeutic usage may have negative effects. Stomach distress, nausea, and vomiting are among them [34].

3.5 Passion Flower: An egg-shaped edible fruit of passionflower (*Passiflora incarnata* L.) is a rich source of vitamins A, C, B_1, and B_2 and calcium, phosphorus, and iron. *Passiflora incarnata* contains alkaloids, phenolic components, flavonoid, and cyanogenic glycosides. Passionflower contains flavonoids such as kaempferol, quercetin, apigenin, and luteolin and flavonoid glycosides like isoorientin, orientin, isovitexin and vitexin [35, 36].

The flavonoids chrysin and/or homoorientin, orientin, vitexin and isovitexin, isolated from *Passiflora incarnata* extracts, have exhibited a strong anxiolytic effect mediated *via* the GABAergic system and are responsible for the hypnotic action [37, 38]. The anti-anxiety properties of *Passiflora incarnata* are analogous to those of benzodiazepines like oxazepam and midazolam. As a result, it appears to be a safe and effective medication for minimising stress reactivity, insomnia, anxiety and depression-like behaviours.

3.6 Valerian Root: The root extract of the valerian plant (*Valeriana officinalis*) is used to alleviate insomnia. The components of valerian inhibit the breakdown of gamma-aminobutyric acid in the brain, causing sleepiness and a decrease in central nervous system activity in mice [39, 40].

3.7 Lemon Balm: *Melissa officinalis*, also known as lemon balm, is an edible annual herbaceous plant native to Europe.

Lemon balm contains rosmarinic acid, which has relaxing actions. By suppressing GABA-transaminase (GABA T), an enzyme that degrades GABA, the traditional relaxation properties may be related to enhanced levels of the neurotransmitter GABA (-aminobutyric acid). Rosmarinic acid is thought to be responsible for this effect [41].

Lemon balm promotes cognitive function and mental wellness and reduces the long-term adverse physiological consequences of stress on personal well-being. Lemon balm has a pleasant flavour and is soluble in water. It can be included in both food supplements and drinks [41].

CONCLUSION: Stress is a common problem that we all have to deal with in life, more than any other. In this report, the factors that put stress on the human body, surroundings and daily life and their impact on health are discussed in detail.

The food that a person eats as part of their daily lifestyle can be used as a tool to overcome or reduce the effects of stress on the body. Unhealthy diets increase stress levels and can lead to more problems if not addressed in the future. One of the most important factors in good health, perhaps most important is a balanced nutrition plan.

A balanced diet plays an important role when we are under stress. When stress occurs, a well-balanced diet and a good mood will increase the resistance to the effects of stress on the body. Stress is going to happen at some point in a person's life, and it will definitely happen more than once. However, because stress is sometimes unavoidable, it is always a choice.

One can either allow the body to suffer from the effects of stress, or we may choose to do something about it. Thus to keep the body and mind healthy, every person should know that nutrition plays an important role in stress management.

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