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BRIDGING HERBAL, SYNTHETIC, AND NON-PHARMACOLOGICAL APPROACHES FOR STRESS: DIAGNOSTICS AND THERAPEUTIC IMPACT

Preeti Jaiswal[1]*, Sagar Debnath[2], Priyanshu Raghav[3], Ms. Cheshta Rawat[4]

[1,2,3]Scholar, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University, Dehradun, India.

[4]Assistant Professor, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University, Dehradun, India.

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***Corresponding Author**

Preeti Jaiswal

Scholar, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University, Dehradun, India.

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ABSTRACT

Stress is a pervasive global health concern with far-reaching psychological, neuroendocrine, and physiological consequences. The World Health Organization (WHO) estimates that more than one billion people worldwide suffer from mental health disorders, including stress-related conditions such as anxiety and depression. This review comprehensively explores the classification, clinical manifestations, and intricate pathophysiology of stress, including dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and neurotransmitter alterations. Diagnostic approaches encompassing psychological assessment tools (Perceived Stress Scale, Stress Appraisal Measure), biochemical and hormonal indicators (cortisol, emotional biomarkers), and neurophysiological techniques (EEG) are discussed. Both pharmacological and non-pharmacological interventions are reviewed, including herbal medicines (Ashwagandha, Rhodiola, Tulsi, Brahmi, Ginseng), synthetic drugs (SSRIs, SNRIs, benzodiazepines, beta-blockers), and evidence-based therapies (CBT, MBSR, ACT). A comparative analysis of herbal versus synthetic approaches is presented, highlighting the benefits and limitations of each. The review concludes that an integrated, personalized approach combining herbal, synthetic, and

non-pharmacological strategies offers the most promising direction for comprehensive stress management.

KEYWORDS: Stress, Herbal medicine, Adaptogen, HPA axis, Synthetic drugs, Anxiety, Non-pharmacological therapy, Cortisol, Neurotransmitters, Stress management.

1. INTRODUCTION

The World Health Organization (WHO) says that a lot of people around the world have mental health problems. According to new data from the World Health Organization (WHO), more than one billion people around the world have mental health disorders. These illnesses include stress-related ailments like anxiety and depression, and they are a major source of disability and poor functioning in all parts of the world (WHO, 2025).[1]

The Global Burden of Disease (GBD) 2019 study revealed that mental disorders continued to rank among the top ten primary causes of global health burden, with no indication of a decrease in total impact since 1990.

The GBD figures also show that a lot more individuals are affected: for example, the number of people with anxiety disorders went from around 311 million in 1990 to 458 million in 2019, and the number of people with depression went from 172 million to 279 million in the same time period.[2]

Even while synthetic drugs are commonly used to treat stress-related problems, there are still big worries about how safe and tolerable they are over the long run. Doctors often prescribe SSRIs, SNRIs, and benzodiazepines to help with stress, anxiety, and depression. These drugs are often linked to side effects include drowsiness, cognitive impairment, sexual dysfunction, weight gain, tolerance, and dependence, especially when used for a long time.[3]

Moreover, vulnerable groups including the elderly, students, and working adults may be more affected by the negative effects of synthetic medications, which raises the need for safer and more tolerable options. In low- and middle-income nations, restricted access to psychiatric care and high treatment costs make it even harder to use conventional drugs effectively. This shows how important it is to have affordable and easy-to-find therapeutic solutions.[1]

In light of these problems, there is increasing interest in safer therapeutic techniques that can be utilized as alternatives or adjuncts to traditional pharmaceutical treatment. Herbal

medicines, dietary supplements, and other complementary therapies are being investigated more and more since they have been used for a long time, are thought to be safe, and new scientific information is coming to light. A review of herbal medications for stress management says that some of them have positive impacts on stress biomarkers and psychological outcomes with fewer negative effects.[4]

2. CLASSIFICATION AND CLINICAL MANIFESTATIONS OF STRESS

2.1 Types of Stress

Stress can be classified based on its duration, nature, and impact on individuals.

A. Based on Duration

Acute stress: Acute stress is a brief reaction to imminent obstacles or perceived dangers. It is characterized by a sudden onset and the potential to momentarily disrupt mental equilibrium; however, it typically subsides rapidly upon the removal of the stressor.

Episodic Acute Stress: Repeated episodes of acute stress are indicative of episodic acute stress. Individuals who are affected by it frequently encounter distressing situations, which can have a detrimental impact on their mental and physical well-being.

Chronic stress: Chronic stress is a long-term condition that is the result of continuous exposure to stressors, such as work pressure, financial difficulties, or personal problems. It may result in severe health complications if not effectively managed.

B. Based on Nature of Stressor

Emotional Stress: Emotional stress is a result of challenging life circumstances, work-related pressure, or interpersonal conflicts. It has a substantial impact on emotional well-being and may be more severe than other forms of stress.

Physical Stress: Directly affecting the body's physiological functioning, physical stress is the consequence of factors such as illness, injury, fatigue, or environmental strain.

Psychological stress: Cognitive and emotional processes are influenced by psychological stress, which is associated with internal mental states such as anxiety, frustration, wrath, trauma, or depression.

Psycho-spiritual Stress: This type of stress arises when an individual's personal values, beliefs, and life circumstances are in conflict, resulting in an internal sense of dissatisfaction or imbalance.

Eustress: Eustress is a positive form of stress that contributes to the effective adaptation to challenges by increasing motivation, performance, and productivity.[5]

2.2 Signs and Symptoms

2.2.1 Symptoms of the body

Migraine

Sleep disturbances

2.2.2 Emotional or psychological symptoms

Experiences of anxiety or apprehension Fury Having difficulty maintaining focus Depression.

2.2.3 Symptoms related to appetite or behavior

Absence of appetite (loss of interest in sustenance) Enhanced appetite.

2.2.4 Serious consequence

Burnout is characterized by a loss of interest in routine tasks.[6]

3. PATHOPHYSIOLOGY OF STRESS

3.1 Neuroendocrine Alterations

3.1.1 Dysregulation of the Hypothalamic–Pituitary–Adrenal (HPA) Axis

Stress→ CRH/AVP→ ACTH→ Cortisol

During stress, our brain's hypothalamus sends out chemical signals called corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). These hormones make the pituitary gland release adrenocorticotropic hormone (ACTH), which makes the adrenal cortex release cortisol, the primary stress hormone.[7]

3.1.2 Activation of the Sympathetic–Adreno-Medullary (SAM) System

When you're under stress, the sympathetic nervous system is activated at the same time, which causes the adrenal medulla to quickly release adrenaline and noradrenaline. These catecholamines control the "fight-or-flight" response by making the heart beat faster, raising blood pressure, and making more energy available.[8][9]

3.2 Changes in Neurotransmitters

3.2.1 Problems with the Serotonergic System

Long-term stress lowers the production of serotonin and changes how sensitive serotonin receptors are, especially in the hippocampus and prefrontal cortex.[10]

3.2.2 Changes in the Dopaminergic System

Long-term stress stops dopamine signaling in the mesolimbic and mesocortical pathways. This causes anhedonia, less drive, and worse cognitive performance.[7]

3.2.3 Hyperactivity of Noradrenergic Neurons

Activation of neurons in the locus coeruleus increases alertness but may also contribute to anxiety and hyperarousal.[8]

3.2.4 An imbalance between GABA and glutamate

Stress diminishes inhibitory GABAergic neurotransmission while augmenting excitatory glutamatergic activity.[7]

Too much glutamate release leads to excitotoxicity and changes in synapses, which makes people more likely to have anxiety and depression.[10]

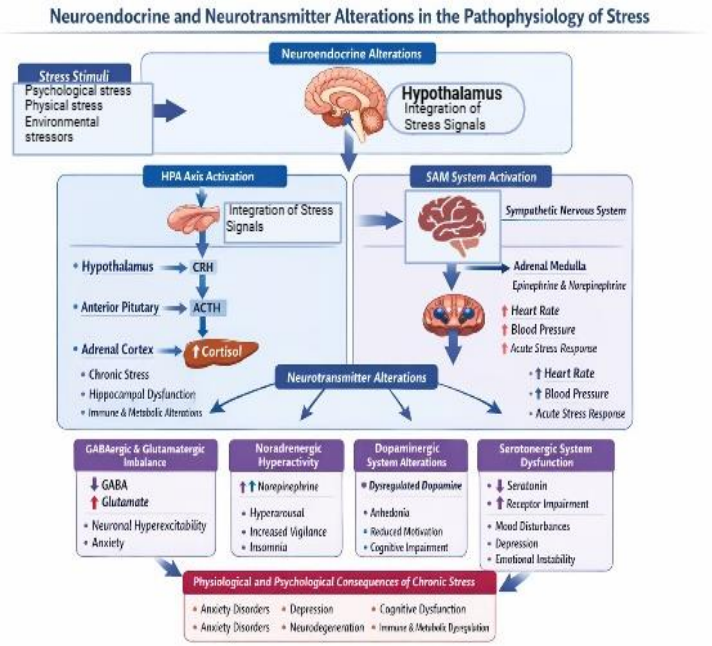

FIG:-Neuroendocrine And Neurotransmitter Alterations In The Pathophysiology Of Stress.

4. DIAGNOSTIC APPROACHES FOR STRESS

4.1 Instruments for Psychological Assessment

4.1.1 Self-Report Scales (Perceived Stress Scale – PSS)

Mental stress assessment is a difficult task due to the fact that stress is experienced and responded to by individuals in a variety of ways. The precision of stress measurement is significantly influenced by the design of the assessment instrument and the method of analysis. Subjective methods have been employed to assess tension in the past. Self-report questionnaires are the most frequently employed among these. The Perceived Stress Scale (PSS) is a widely used instrument that assesses the extent to which individuals perceive stressful situations in their lives.[11]

4.1.2 Stress Appraisal Measure (SAM)

The Stress Appraisal Measure (SAM) assesses the cognitive interpretation of stressful events by individuals. It concentrates on two critical elements.

Primary evaluation: determining whether a situation is perceived as a threat, challenge, or damage Secondary evaluation: the assessment of the available resources for managing SAM offers a perspective on the manner in which individuals perceive stress and the extent to which they believe they can effectively manage it.[12]

4.2 Hormonal and Biochemical Indicators

4.2.1 Hair Cortisol as a Stress Indicator

When the hypothalamic–pituitary–adrenal (HPA) axis is activated, the adrenal medulla releases cortisol, a glucocorticoid hormone. As a result of its elevated levels during stressful circumstances, it is frequently referred to as the "stress hormone." The measurement of cortisol levels in hair is a valuable tool in psychoneuroendocrine research because it provides a reliable, long-term indicator of chronic stress exposure.[13]

4.2.2 Biomarkers of Emotional Stress

The central nervous system regulates emotional states through intricate chemical and neurological processes. These mechanisms have an impact on emotions such as contentment, sadness, and happiness. Mood swings, impulsive behavior, and intense emotional reactions are indicators of emotional tension and dysregulation. Mental health disorders, such as major depressive disorder, can be exacerbated by prolonged emotional tension. Furthermore, the

brain may activate neurodegenerative pathways by responding to emotional duress in a manner that is comparable to physical trauma.[14]

4.3 Neurophysiological Techniques

4.3.1 Neurophysiological Test (EEG)

Electroencephalogram (EEG) signals are extensively employed in bioengineering research and clinical diagnosis to investigate brain activity. Psychophysiology, psychology, and interactive technologies are among the disciplines in which EEG-based systems can be implemented.

The development of systems that classify various tension levels using EEG data has been facilitated by recent advancements. Tasks such as the Stroop color-word test are employed in experimental settings to generate varying degrees of tension. The tension detection methods are subsequently validated by analyzing the collected EEG signals. These methods have resulted in the development of real-time stress-monitoring systems that are based on EEG analysis.[15]

5. PHARMACOLOGICAL INTERVENTIONS FOR STRESS MANAGEMENT

Table 1: Herbal Medicines in Stress Management.

S. No.	Herbal Medicine (Botanical Name)	Active constituents	Uses	Mechanism of Action (MOA)	Reference
1	Ashwagandha (Withaniasomnifera)	Withanolides (withaferin A, withanolides A-Y), O-glycosylated withanolides (sitoindosides),	Anti-stress, Anti-inflammatory, Anti-tumor, Anti-oxidant, Immunomodulatory, Hemopoetic, Rejuvenating effect.	Ashwagandha works by enhancing neurotransmitter function and modulating GABA receptor activity, helping regulate the body's stress and anxiety response.	[16] [17] [18]
2	Rhodiola (Rhodiola rosea)	Phenylpropanoids: rosavin, rosin, rosarian, salidroside (rhodioloside), tyrosol, rodiolin, etc	Reduces stress, depression enhances energy level, reduces anxiety symptoms,anti-inflammatory	Rhodiola reduces stress by modulating HPA-axis hormones and regulating hypothalamic stress-related gene expression.	[19] [4] [20] [21]
3	Holy Basil / Tulsi (Ocimum sanctum)	Eugenol, ursolic acid, rosmarinic	Neuro-protective, cardio-protective,	Modulates stress hormones,	[22] [23] [16]

		acid	antimicrobial, antiviral, antifungal, anti-oxidant	Balancing neurotransmitters, and providing antioxidant, anti-inflammatory effect	
4	Brahmi (Bacopamonnieri)	Bacosides A and B, saponins	Reduces anxiety and Stress, cognitive calm, Memory enhancer, cognitive support, antioxidant	Modulates neurotransmitters, antioxidant, neuroprotective	[24]
5	Ginseng (Panax ginseng)	Ginsenosides, polysaccharides	Adaptogen, reduces stress/fatigue, Boosts immunity, improves stamina, enhances sexual health	Ginsenosides modulate HPA axis, neurotransmitters, antioxidant	[16] [25]
6	Nyctanthesarbor-tristis (Parijat / Harsingar)	Quercetin, Astragalin, Nicotiflorin, Arbortristoside-A, Arbortristoside-B	Anti-stress & Anxiolytic, Antipyretic, Anti-inflammatory, Analgesic	Depression of central nervous system activity → decreased spontaneous motor activity → reduced mental excitation and anxiety → calming and anti-stress effect.	[43] [44]
7	Passionflower (Passiflora incarnata)	Flavonoids (chrysin), alkaloids	Anxiety reduction, calming effects, Sleep aid, mild sedative,	GABA modulation, reduces anxiety	[16]
8	Valerian Root (Valeriana officinalis)	Valerenic acid, valepotriates	Reduces anxiety and stress, Sleep disorders, relaxant, muscle spasms	Increases GABA, sedative, anxiolytic	[16]

Table 2: Synthetic Drugs Used in Stress and Anxiety Disorders.

S.No	Category	MOA	Uses	Side Effect	Reference
1	SSRIs: Fluoxetine Sertraline Citalopram	Selective 5-HT reuptake inhibitor	Major depression, OCD, Panic disorder, Social phobia	GI symptoms (nausea, diarrhoea), CNS (anxiety, tremor, somnolence), Sexual dysfunction	[26] [27]
2	SNRIs: Duloxetine Venlafaxine (XR)	5-HT, NE and DA reuptake inhibitor	Major depression, Anxiety disorders	Nausea, constipation, Insomnia, somnolence, dizziness	[26] [28]

	Desvenlafaxine		(GAD, social anxiety, panic, PTSD, OCD)		
3	TCAs: Clomipramine Imipramine Desipramine	NE and 5-HT reuptake inhibitor	Major Depressive Disorder	Dry mouth, constipation, blurred vision,	[26] [29] [30]
4	Benzodiazepines: Clonazepam Alprazolam Lorazepam	GABA-A agonist	Reduce anxiety, sleep problems, stop seizures, muscle spasms and spasticity	Dependence and addiction, Drowsiness and sedation, Memory problems and poor concentration	[26] [31]
5	Beta-blockers: Propranolol	β-1, β-2 antagonist	Heart attack, Hypertension, Congestive Heart Failure	Fatigue, slow heart rate, cold extremities	[26] [32]

6. NON-PHARMACOLOGICAL INTERVENTIONS FOR STRESS MANAGEMENT

6.1 Cognitive Behavioral Therapy (CBT): CBT is a primary stress-management technique that helps people find and change harmful beliefs and behaviors. Meta-analyses show that CBT greatly lowers workers' stress, anxiety, and depression at work.[33]

6.2 Mindfulness-Based Stress Reduction (MBSR) and Mindfulness Interventions: Mindfulness-based programs encourage you to be aware of and accept the present moment. MBSR is an 8-week group program that includes meditation, body scanning, and mild yoga. It is specifically designed to help people become more aware and less stressed.[34]

6.3 Acceptance and Commitment Therapy (ACT): ACT is a type of CBT that focuses on acceptance and taking action based on your beliefs. The main goal is to make people more psychologically flexible, which means they can behave in keeping with their ideals even when they have bad thoughts or feelings.[35]

6.4 Other Evidence-Based Approaches: There are other non-drug ways to relieve stress than CBT, MBSR, and ACT: Stress Management Training / Relaxation: Progressive muscle relaxation, guided visualization, and breathing exercises are all traditional ways to relax that reliably lower stress and anxiety. A meta-analysis of relaxing for anxiety indicated results that were medium to large.[36]

7. COMPARATIVE ANALYSIS: HERBAL VS SYNTHETIC THERAPIES

Adaptogenic plants are the main ingredients of herbal stress management therapies. These plants help the body deal with stress from physical, mental, and environmental sources. These substances work in several ways, such as by controlling the hypothalamic-pituitary-adrenal (HPA) axis, lowering cortisol levels, changing the levels of neurotransmitters like serotonin, dopamine, and gamma-aminobutyric acid (GABA), and lowering oxidative stress and inflammation. Withaniasomnifera (Ashwagandha), Panax ginseng, Ocimum sanctum (Tulsi), Rhodiola rosea, and Valeriana officinalis are some of the most common herbal anti-stress medications. Clinical and experimental research show that these herbs can help with stress, anxiety, exhaustion, and cognitive impairment caused by stress, especially when stress levels are low to moderate. Herbal therapies are usually safe, can be used for a long time, and have fewer side effects. However, they are not widely accepted in conventional medicine because of problems like differences in phytochemical composition, lack of standardization, delayed nset of action, and possible interactions between herbs and drugs.[37][38][39]

Synthetic medicines for stress management comprise chemically synthesized pharmacological compounds engineered to exert particular and targeted effects on central nervous system pathways associated with stress and anxiety. Benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), beta-blockers, and other medications that help with anxiety or depression are some of these. Benzodiazepines work by making GABA-A receptors more active, which quickly relieves anxiety and sedates. SSRIs and SNRIs, on the other hand, reduce stress by making serotonergic and noradrenergic neurotransmission stronger. Synthetic pharmaceuticals are quite helpful for moderate to severe stress-related disorders, like generalized anxiety disorder and depression. They also work faster than herbal therapies to relieve symptoms. But people often can't use them for long periods of time since they can cause problems like sedation, cognitive impairment, sexual dysfunction, withdrawal symptoms, and a higher chance of becoming dependent on them, especially with benzodiazepines. Because of this, synthetic therapies need to be supervised by a doctor and are usually only indicated for short-term or clinically diagnosed disorders, not for managing stress on a regular basis.[40][41][42]

8. FUTURE PERSPECTIVES

Even though we know a lot more about the neurobiological causes of stress and have both herbal and synthetic treatments available, there are still certain problems that need to be

solved through more research. One of the most important things to do is to make sure that herbal and synthetic medicines are part of tailored, evidence-based treatment plans. Using standardized herbal remedies along with synthetic pharmaceuticals in combination may assist lower drug doses, reduce side effects, and enhance long-term treatment adherence, especially for people with chronic stress and anxiety disorders.

To find out how well herbal medicines work, how safe they are, and what the best dose is, future research should focus on large-scale, randomized controlled clinical studies. While some herbal medicines, including Withaniasomnifera, Rhodiolarosea, and Panax ginseng, exhibit encouraging anti-stress properties, their broader clinical acceptability is hindered by diversity in phytochemical composition, absence of standardization, and insufficient pharmacokinetic data. New phytopharmaceutical technologies, such as marker-based standardization, new ways to distribute drugs, and quality control approaches, may make herbal compositions much more reliable and consistent in their effects.

Another key future direction is finding accurate biomarkers that may be used to diagnose stress and keep an eye on treatment. The combination of biological markers (such cortisol and inflammatory cytokines), neurophysiological methods (like EEG-based stress profiling), and psychological assessment scales should make it possible to find problems early on and objectively measure how well treatments are working. Furthermore, the increasing interest in digital health technology, such as wearable stress-monitoring devices and mobile-based mental health therapies, may enhance pharmacological and non-pharmacological stress management approaches.

Moreover, forthcoming stress treatment frameworks ought to include a comprehensive and interdisciplinary methodology, integrating medication, herbal medicine, psychotherapy, and lifestyle alterations. Long-term safety, affordability, and accessibility of therapy are very important for vulnerable groups like students, the elderly, and working professionals.

9. CONCLUSION

Stress is a widespread global health issue with significant psychological, neuroendocrine, and physiological effects. This review emphasizes the intricate pathophysiology of stress, characterized by disruption of the HPA axis, modifications in neurotransmitter systems, and prolonged activation of neuroendocrine pathways. SSRIs, SNRIs, and benzodiazepines are examples of traditional synthetic medications that are still the best way to treat moderate to

severe stress-related problems since they work quickly and effectively. But its long-term usage is generally limited by side effects, tolerance, and the chance of becoming dependent.

Herbal medicines are a potential way to help with stress, especially in mild to moderate cases. Adaptogenic herbs have effects on more than one target, such as changing the levels of stress hormones, neurotransmitters, and antioxidants, as well as protecting the nervous system. They also tend to be easier to tolerate. Still, problems such a lack of standardization, a slow start to action, and a lack of high-quality clinical evidence make it hard for them to be used widely in medicine.

In conclusion, neither herbal nor synthetic therapies alone offer a comprehensive solution for stress management. A balanced, integrated approach, bolstered by rigorous scientific validation, standardized formulations, and personalized treatment planning, signifies the most auspicious future trajectory. Ongoing research that connects ancient knowledge with modern pharmacological science is necessary to create safer, more effective, and more accessible ways to control stress for the health of the world.

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