WJPMR, 2026, 12(7), 431-439

Review Article

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Impact Factor: 7.533

ISSN (O): 2455-3301

ISSN (P): 3051-2557

Coden USA: WJPMBB

EXPLORING THE STRESS-MODULATORY POTENTIAL OF DUSHIVISHARI AGAD THROUGH ITS PHYTOCONSTITUENTS: A COMPREHENSIVE REVIEW OF PRE-CLINICAL EVIDENCE

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DOI: https://doi.org/10.5281/zenodo.21155141

How to cite this Article: Dr. Rashi Negi[1], Dr. Bhawana Mittal[2*], Dr. Ramesh Chandra Tiwari[3] (2026). Exploring The Stress-Modulatory Potential Of Dushivishari Agad Through Its Phytoconstituents: A Comprehensive Review Of Pre-Clinical Evidence. World Journal of Pharmaceutical and Medical Research, 12(7), 431–439.

Article Received on 05/06/2026 **Article Revised on 25/06/2026** **Article Published on 01/07/2026**

ABSTRACT

As a consequence of modern lifestyle demands, chronic stress has emerged as a significant contributor to psychological and psychosomatic disorders with disturbances in neuroendocrine regulation, immune function, oxidative balance and emotional well-being. In Ayurveda, the chronic effects of stress may be correlated with the concept of *Dushi Visha*, which is a latent toxin that impairs the physiological and psychological homeostasis. *Dushivishari Agad*, a classical Ayurvedic formulation indicated for *Dushi Visha*, is a poly-herbal formulation with documented neuroprotective and adaptogenic properties. This review evaluated the available preclinical evidence on the constituent drugs of *Dushivishari Agad* to explore their potential role in stress modulation. The reviewed studies revealed that the formulation possesses a broad spectrum of biological activities, including antioxidant, adaptogenic, neuroprotective, anti-inflammatory, anxiolytic, nootropic, and gastroprotective effects. The reviewed studies demonstrated that the phytoconstituents of *Dushivishari Agad*, including alkaloids, flavonoids, phenolics, terpenoids, saponins, and essential oils, modulate multiple pathways implicated in chronic stress. The available preclinical evidence supports the potential role of *Dushivishari Agad* as a multitarget stress-modulatory formulation. Further standardization, mechanistic studies, and clinical trials are warranted to validate its efficacy and facilitate its integration into evidence-based stress management strategies.

KEYWORDS: *Dushivishari Agad, Stress, Pre-clinical, Dushi Visha, Ayurveda, Chronic Stress.*

INTRODUCTION

Stress has become an inseparable component of modern living. It is slowly penetrating deeper into society irrespective of age, gender, caste, socio-economic status, and geography. It has emerged as a **"silent epidemic"** of the 21st century as categorized by WHO.[1] Stress has a vital physiological **"fight-or-flight"** mechanism but its chronic activation transitions into chronic stress, that results in dysregulation of the **hypothalamic-pituitary-adrenal (HPA) axis**, alter neurotransmitter balance, induce oxidative stress, and systemic inflammation.[2]

Ultimately, the repetition of this physiological cycle manifests as various psycho-somatic diseases including anxiety, depression, cardiovascular diseases, metabolic disorders, IBS (irritable bowel syndrome), gastric ulcers, and Alzheimer's disease.[3] Chronic stress acts as a bridge between psychological, systemic, and cellular function. While contemporary management relies heavily on psychotherapy, anxiolytics, and antidepressants.[4] These interventions are often limited by adverse effects such as dependency, cognitive impairment, and withdrawal symptoms.[5] Consequently, in recent years there has been a global inclination towards natural, safe and holistic strategies that has revitalized its interest in traditional medicine.

Dushivishari Agad, is a herbo-mineral classical formulation described in *Ashtanga Hrudayam*, traditionally indicated for *Dushi Visha* in *Agadtantra*, a branch of Ayurveda that deals with toxins and its management. *Dushi Visha* is a latent poison that vitiates the body's resilience (*Ojas)* by staying in dormant state for prolonged period and triggers by external stressors. *Dushi Visha* holds resemblance to chronic, long-standing effects of stress.[6] Therefore, ***Dushivishari Agad*** may act as a potent formulation for stress modulation through its ingredients which include herbs like ***Pippali, Dhyamaka, Jatamansi, Lodhra, Ela, Suvarchika, Kuttannata, Natam, Kustha, Yashti, Chandana,*** **and** ***Gairika***, as it possesses a rich profile of bioactive phytoconstituents such as *piperine*, *flavonoids*, *phenolic compounds*, *jatamansic acid*, *terpenoids*, and *saponins.*[7] They are known for their neuroprotective, antioxidant, anti-inflammatory, and immuno-modulatory properties. While, according to Ayurveda, its ingredients are valued for their ***Rasayana*** (rejuvenating), ***Vishaghna***, ***Deepan, Medhya*** (nootropic), ***Unmada nashak*** (psychosis), ***Nidrajanak*** (sleep-inducing), and ***Hrudya*** (cardio-protective) properties. By potentially neutralizing the metabolic by-products or residual toxicity that builds up during chronic emotional and physical stress, this formulation act as a link between ancient toxicology and modern research.[6,8,9]

This review provides a comprehensive evidence-based view of pre-clinical studies and meta-analysis regarding its individual herbal ingredients. It aims to explore the stress-modulatory potential of ***Dushivishari Agad***, by evaluating how its specific phytoconstituents interact with biological pathways to support the body's resilience and reduce the impact of chronic stress on the body.

Pathophysiology of Chronic Stress[10,11]

Chronic stress results from persistent exposure to stressors, resulting in prolonged activation of the hypothalamic-pituitary-adrenal axis (HPA) and sympathetic nervous system. This causes sustained release of corticotropic releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) secretion, cortisol, and catecholamines. While acute stress responses are adaptive, chronic stimulation disrupts the normal HPA axis feedback mechanism, causing cortisol dysregulation, glucocorticoid resistance, and increased an allostatic load, characterized by physiological wear and tear of the body (**Juster et. al., 2010).** Chronic stress alters neuroplasticity in the hippocampus, prefrontal cortex, and amygdala, impairing cognition, memory, and emotional regulation (**Godoy et. al., 2018).** Furhermore, chronic stress promotes autonomic imbalance, oxidative stress, mitochondrial dysfunction, and activation of pro-inflammatory pathways, increasing cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which further activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB). These neuroendocrine, immunological, metabolic, and cardiovascular alterations collectively contribute to the development of psycho-somatic disorders, including anxiety, depression, cardiovascular disease, metabolic syndrome, and impaired immune function**.**

***Dushivishari Agad*[12,13,14]- An anti-toxin for modern disorders**

Table 1: *Dushivishari Agad* according to various *Acharyas.*

Sr. no.	*Vagbhata*	*Sushrut*	*Bhavprakash*
1.	*Pippali*	*Pippali*	*Pippali*
2.	*Dhyamaka*	*Dhyamaka*	*Dhyamaka*
3.	*Jatamansi*	*Jatamansi*	*Jatamansi*
4.	*Lodhra*	*Lodhra*	*Lodhra*
5.	*Ela*	*Paripelava*	*Bruhat ela*
6.	*Suvarchika*	*Suvarchika*	*Suvarchika*
7.	*Kutannata*	*Sukshma Ela*	*Maricha*
8.	*Natam*	*Kanaka Gairika*	*Baalaka*
9.	*Kustham*		*Sukshma Ela*
10.	*Yashti*		*Kanaka Gairika*
11.	*Chandana*		
12.	*Gairika*		

For this review we selected *Ashtang Hrudayokta Dushivishari Agad* formulation which is composed of total 12 ingredients.

Table 1.1: Summary of ingredients and mechanism of stress modulation.

Sr. no.	Ingredient	Pharmacological activities	Stress-relevant mechanism
1.	*Piper longum*	-Antistress, -nootropic, -neuroprotective, -cognitive-enhancing, -bioavailability enhancer	-Decreased VMA, 5-HIAA -Increased HVA, ascorbic acid - Enhances serum concentration, absorption -Increases t max
2.	*Cymbopogon citratus*	-Anti-oxidant, -Gastroprotective	-Reduced ROS -restored cellular redox -improves epithelial integrity -Increased TEER
3.	*Nardostachys jatamansi*	-Anti-stress, -Nootropic, -Anti-oxidant, -Gastroprotective, -Anti-depressant	-Suppression of NF-KB cells -Reduction of nitrite, lipid peroxidation, ROS
4.	*Symplococus racemosa Roxb.*	-Anti-oxidant, -Gastroprotective,	- Reduce lipid peroxidation, -Enhanced superoxide dismustase, catalase activity.
5.	*Elettaria cardamomum Maton.*	-Adaptogenic -Neurotransmitter Modulation, -Anti-inflammatory	-Improved cognitive performance -Reduced β-amyloid deposition, tau hyperphosphorylation, MDA, pro-inflammatory cytokines, - Enhances glutathione, SOD - Reduced (ROS) - Suppresses NF-KB, TNFa, IL-6, COX2
6.	*Cleome viscosa Linn.*	-Anti-inflammatory	-Inhibition of COX-1, lipid peroxidation
7.	*Oroxylum indicum Linn.*	-Anti-oxidant -Gastroprotective -Anti-inflammatory	-Inhibited AGEs, TLR4-mediated inflammatory signalling -Suppressed inflammatory mediators
8.	*Valleriana jatamansi Jones*	-Neuroprotective -Cognitive-enhancing -Anxiolytic -Sedative	-Enhanced GABA-A1 receptors -Improves sleep and emotional regulation
9.	*Sassurea lappa C.B.*	-Anti-oxidant -Gastroprotective	- Inhibition of inflammatory enzymes - Neutralizing ROS -Inhibition of radical free scavenging
10.	*Glycyrrhiza glabra Linn.*	- Anti-stress - Adaptogenic	-Reduced lipid peroxidation, - Restored endogenous SOD, catalase - Increased swimming time, locomotor activity, and motor coordination, resistance to fatigue and stress
11.	*Pterocarpus santalinus l.f.*	-Neuroprotective -Cognitive enhancing	-Reduced AChE
12.	Red ochre	-Anti-oxidant -Gastroprotective	- Promoted the growth of beneficial gut bacterias -Showed free radical scavenging activity

PHARMACOLOGICAL & PRE-CLINICAL RESEARCH FINDINGS

The pharmacological and pre-clinical research findings of ingredients of *Dushivishari Agad* validates its therapeutic potential through its active phytoconstituents and their interaction with the biochemical pathway. These pre-clinical findings are derived from in-vitro and in-vivo research, demonstrating stress modulation action by the ingredients such as anti-oxidant, anti-stress, anti-inflammatory, adaptogenic, neuroprotective, and anti-anxiety effects. The formulation is enriched with polyphenols, alkaloids, terpenoids, flavonoids, and essential oils. These compounds have been recognized as an antioxidant, through its free radical scavenging activity and chelating process as it performs stress modulation activity.[15]

STRESS MODULATIVE ACTION OF DUSHIVISHARI AGAD

1) Anti-stress & Nootropic

a) PIPPALI[16]- Kilari et al. (2015) investigated the anti-stress and nootropic activity of aqueous fruit extract of *Piper longum* in rodents using the models forced swim and Y-maze test at doses of 100, 200, and 300 mg/kg, per

oral. The extract showed **significant dose-dependent anti-stress activity** by decreasing urinary vanillylmandelic acid (VMA) and 5-hydroxyindoleacetic acid (5-HIAA), indicating attenuation of stress-induced catecholaminergic and serotonergic overactivity. Simultaneously, it increased homo vanillic acid (HVA) and ascorbic acid levels as compared to stress-induced animals, suggesting improved dopaminergic neurotransmission and enhanced antioxidant defence. At **300 mg/kg**, the biochemical parameters were restored nearly to normal levels. The extract also significantly improved locomotor activity, spontaneous alternation behaviour, and working memory in a scopolamine-induced cognitive impairment, along with marked free radical scavenging activity. Due to the presence of piperine and piperlongumine, metabolites were reduced and dopaminergic activity increased, which may contribute to the improvement in anxiety, irritability, and sleep disturbances. This study establishes the antioxidant-mediated anti-stress and nootropic effects of *Piper longum*.

b) JATAMANSI[17,18] - Joshi H. et al. (2006) reported administration of ethanolic extracts of *Nardostachys jatamansi* to young and aged mice. The **elevated plus maze** and the **passive avoidance paradigm** models were employed to evaluate learning and memory parameters. Three doses (50, 100, and 200 mg/kg, p.o.) were administered for 8 successive days. 200mg/kg dose of ethanolic extract significantly improved learning and memory in young mice and reversed age-related amnesia in older mice. The study suggested that the plant possesses notable cognitive-enhancing and neuroprotective properties. The nootropic activity is attributed to its phytoconstituents such as *sesquiterpenes, jatamansone* and other volatile compounds, which are believed to modulate neurotransmitter systems through the suppression of NF-kB signalling pathway and reduce oxidative stress. Its phytoconstituents such as coumarins and several sesquiterpenoids consists of essential oils that have the ability to cross the blood-brain barrier and therefore *N. jatamansi* demonstrated a significant **nootropic** and **memory restorative activity**.

c) YASHTI[19]- Sowmya and Sathish Kumar (2010) investigated the antistress activity of *Glycyrrhiza glabra* using a methotrexate (MTX)-induced stress model in *Drosophila melanogaster*. Stress was induced by supplementing the fly culture media with MTX at concentrations ranging from 5–25 ppm, it significantly elevated oxidative stress markers. The antistress activity was assessed by estimating the activities of endogenous antioxidant enzymes **superoxide dismutase (SOD)** and **catalase (CAT)**, which serve as biochemical markers of oxidative stress through MTX exposure. However, supplementation with *G. glabra* powder significantly reduced the elevated SOD and CAT activities in stressed flies, suggesting attenuation of oxidative stress and restoration of redox homeostasis. The study demonstrated that *G. glabra* effectively counteracted MTX-induced oxidative stress in *Drosophila melanogaster*, thereby establishing its significant **antistress and antioxidant** potential, likely mediated by glycyrrhizin and flavonoids.

2) Adaptogenic & Neurotransmitter Modulation

a) **YASHTI[20]- Prabhuram et al. (2011)** investigated the adaptogenic activity of methanolic root extract of *Glycyrrhiza glabra* in **Wistar rats** using **swimming endurance test, cold restraint stress model, and nitric oxide scavenging assay** at oral doses of 100, 200, and 400 mg/kg. In the swimming endurance model, the extract significantly increased swimming time, locomotor activity, and motor coordination while normalizing stress-induced changes in adrenal gland weight and serum biochemical parameters including glucose, cholesterol, and triglycerides, indicating improved resistance to **fatigue** and **stress** along with better physical performance under stress. In the cold restraint stress model, it significantly attenuated stress-induced haematological and metabolic disturbances, reduced lipid peroxidation, restored endogenous antioxidant enzymes including superoxide dismutase (SOD) and catalase (CAT), and protected against adrenal histopathological alterations. The extract also demonstrated significant nitric oxide scavenging activity in vitro. The 400 mg/kg dose exhibited maximal adaptogenic activity, indicating that *Glycyrrhiza glabra* exerts significant stress-modulatory, antioxidant, and adrenal protective effects, likely mediated through glycyrrhizin, flavonoids, and triterpenoid saponins through their **antioxidant and adaptogenic** properties.

3) Neuroprotective & Cognitive-Enhancing Activity

a) PIPPALI[21]- In an in vivo study by **Ying Bi et al. (2015)**, alkaloids isolated from *Piper longum* (PLA), contains 54.1% piperine, 3.74% piperlonguminine, and 0.62% Δα, β-dihydro piperlonguminine in an MPTP-induced Parkinsonian mouse model. Oral administration of *Piper longum* alkaloids, particularly at 60 mg/kg, significantly improved locomotor activity, increased striatal dopamine (DA) and DOPAC (3,4-dihydroxyphenylacetic acid) levels suggestive of enhanced neurotransmission, which is crucial for stress adaptation, motivation, and cognition, while elevated endogenous antioxidant markers such as glutathione (GSH) and superoxide dismutase (SOD), and reduced malondialdehyde (MDA) reflects strengthened antioxidant defenses and protection against free radical-induced neuronal injury. Pharmacokinetic experiments also demonstrated that the oral bioavailability of *PLA* is higher than piperine **(Liu et al., 2011).** Therefore, we speculate that *PLA* may have pleiotropic effects. This study concluded that *Piper longum* possesses significant neuroprotective and antioxidant properties, suggesting its potential role in modulation of stress-associated neurochemical disturbances.

b) TAGAR[22]- Sridharan et al. (2015) investigated the neuroprotective effect of *Valeriana wallichii* rhizome

extract in MPTP-induced Parkinsonian C57BL/6 mice at doses of 50, 100, and 200 mg/kg for 14 days. The extract significantly improved behavioural deficits, restored striatal dopamine levels, increased tyrosine hydroxylase-positive neuronal cell count, and attenuated histopathological alterations in the midbrain. The treatment also significantly reduced reactive oxygen species (ROS), lipid peroxidation, and pro-inflammatory cytokines, while enhancing endogenous antioxidant defenses including glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and glutathione reductase (GR). Restoration of dopamine levels and preservation of dopaminergic neurons suggest improvement in neuronal signalling involved in motor function, cognition, motivation, and stress adaptation, whereas reduction in oxidative stress and neuroinflammation indicates protection against free radical-mediated neuronal injury. The 200 mg/kg dose exhibited maximal neuroprotection, suggesting phytoconstituents such as valepotriates, sesquiterpenes, and flavonoids present in *V. wallichii* exerts significant antioxidant, anti-inflammatory, and dopaminergic neuroprotective effects against oxidative stress by attenuating neuroinflammation.

c) ELA[23]- Gomaa et al. (2019) demonstrated neuroprotective effects of *Elettaria cardamomum* extract, it is rich in terpenoids and the study was performed on Alzheimer-like alterations in rats with type 2 diabetes mellitus (T2DM). EC extract was administered for 8weeks which significantly improved cognitive performance, reduced β-amyloid deposition, tau hyperphosphorylation, oxidative stress marker malondialdehyde (MDA), pro-inflammatory cytokines **(Tumor necrosis factor alpha, IL-1β),** and **Glycogen synthase kinase 3 beta** activity in diabetic rats, while enhancing endogenous antioxidant defenses including glutathione (GSH) and superoxide dismutase (SOD). The model used was **passive avoidance task** and **morris water maze test.** It suggests that terpenoid-rich cardamomum extract could be a therapeutic agent for diabetes-associated cognitive decline and Alzheimer-like neurodegeneration by scavenging reactive oxygen species, and suppressing pro-inflammatory cytokine production. Such actions may contribute to the alleviation of stress-associated manifestations such as memory deficits, impaired learning, and mental fatigue. **(Ref-)**

d) RAKTA CHANDANA[24]- Biswas et al. (2018) evaluated the cholinesterase inhibitory and memory-enhancing activity of **methanolic bark extract** of *Pterocarpus santalinus* in scopolamine-induced amnesic mice. The extract was administered intraperitoneally at dosages of **100, 200, and 400 mg/kg for 7 days** and it showed significant improved memory retention in the **passive avoidance test** while reducing elevated brain acetylcholinesterase **(AChE)** activity. In vitro, the extract showed significant AChE inhibitory activity. Reduction of **AChE** activity suggests an increased availability of acetylcholine in the synaptic cleft, thereby facilitating cholinergic neurotransmission, which plays a crucial role in learning, memory, and cognitive processing. The **400 mg/kg dose exhibited maximal neuroprotective effect**, attributed to *terpenoids, phenolics, β-sitosterol, lupeol, and pterostilbene* present in the bark extract, suggesting its therapeutic potential against Alzheimer's disease and potentially in counteracting stress-related cognitive decline.

4) Anti-oxidant & Gastroprotective activity

a) DHYAMAKA[27,28,29]- Toschi et al. (2011) investigated the effect of phenol-rich botanical extracts on **human intestinal epithelial (Caco-2) cells** under oxidative stress conditions. The study demonstrated that phenolic constituents significantly **reduced intracellular reactive oxygen species (ROS) generation**, restored cellular redox balance, and improved **epithelial barrier integrity** by enhancing the tight-junction protein expression and increasing **transepithelial electrical resistance (TEER)**. **S uzuki et. al. 2011**. Since *Cymbopogon citratus* is rich in phenolic compounds, these findings suggest that its phenolic constituents may contribute to protective against oxidative damage and against inflammation in the epithelial cells, thereby supporting their potential **antioxidant and gastroprotective effects.**

b) KUSTHA[30]- Aati et al. (2022) evaluated the phytochemical composition and in vitro pharmacological activities of *Saussurea lappa* root extracts using **GC–MS** and **LC–MS** analyses. The study identified several bioactive constituents, including the sesquiterpene lactones costunolide and dehydrocostus lactone, along with phenolics and flavonoids. The extracts exhibited significant antioxidant activity through free radical scavenging, reducing power assays, as well as notable anti-inflammatory effects via inhibition of inflammatory enzymes. By neutralizing reactive oxygen species and limiting inflammatory responses, *S. lappa* may help protect cells from oxidative stress–induced damage. indicating potent antioxidant and cytoprotective effects. The study demonstrated that sesquiterpene lactones in *S. lappa* are the major contributors to these biological effects, supporting its potential role in cytoprotection, stress modulation, and neuroprotection.

5) Sedative and Anti-depressive activity

a) TAGAR[33]- Phytochemical investigations of *Valeriana wallichii* have identified bioactive flavonoids, particularly **6-methylapigenin** and **(2S)-hesperidin**, which exhibit sedative and anxiolytic properties through modulation of **Gamma-aminobutyric acid receptors subunit alpha-1**, 6-methylapigenin has been shown to enhance the sleep-enhancing effect of hesperidin, indicating a synergistic action on inhibitory neurotransmission. Supporting these mechanistic findings**, Sahu et al. (2012)** demonstrated that the aqueous root extract of *V. wallichii* significantly improved sleep quality and modulated cortical and

brainstem monoamine levels in rats, suggesting its influence on neurotransmitter systems involved in sleep and emotional regulation. These findings establish the sedative activity of V. wallichii and support its potential role in stress by reducing hyperarousal, promoting restful sleep, and improving neurochemical balance.

b) JATAMANSI[34]- Sahu R. (2016) demonstrated dose-dependent (200 and 400mg/kg) antidepressant activity of N. *jatamansi* root extract in male swiss mice using the tail suspension and forced swim tests. The extract significantly altered the levels of central monoamines, inhibitory amino acid, gamma-amino butyric acid (GABA), serotonin, taurine and 5-hydroxy indoleacetic acid levels, indicating modulation of neurotransmitter systems involved in mood regulation. The finding suggested that dose-dependent **antidepressant activity** is present in *Nardostachys jatamansi*. Since chronic stress is often associated with disturbances in monoaminergic and GABAergic signalling, these findings suggest that N. jatamansi may provide contribution to stress alleviation through restoration of neurochemical balance.

6) Anti-inflammatory activity

a) LODHRA[35]- Sharma et. al. (2013) evaluated the analgesic activity and anti-inflammatory activities of ethanolic and aqueous bark extracts of *Symplococos* using formalin induced paw licking and tail flick models for analgesia and carrageenan-induced hind paw edema for inflammation. Their results revealed that ethanolic extract produced a significant in pain threshold and markedly suppressed carrageenan-induced edema compared with the aqueous extract. The prolonged inhibition of inflammation suggests interference with inflammatory mediators**.** Since chronic stress is frequently associated with activation of inflammatory pathways and increased oxidative burden, the anti-inflammatory activity of *S. racemosa* may contribute to stress alleviation by limiting inflammation mediated tissue damage and restoring physiological homeostasis.

b) ELA[36]- Sreedharan et. al. (2023) investigated the anti-inflammatory activity of methanolic extracts of *Elettaria cardamomum* and reported high levels of phenolic and terpenoid content in the whole cardamom, seeds, skin fractions exerted significant anti-inflammatory effects in lipopolysaccharide (LPS) stimulated bacteria in colon and macrophage cells. The extracts reduced reactive oxygen species (ROS) generation and suppressed the expression of pro-inflammatory mediators, including **nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)**, TNFα, IL-6, and COX2. In macrophages, cardamom extracts also enhanced the expression of nuclear receptors LXRα and PPARγ. By attenuating oxidative stress and inhibiting NF-κB-mediated inflammation. It may help protect against stress-induced cellular damage and chronic low-grade inflammation, supporting its potential role in stress modulation.

c) SUVARCHIKA[37]- Recent phytochemical investigations by **Dissanayake et al. (2022)** identified terpenoid and steroidal compounds isolated from *Cleome viscosa* leaves, including malabaric acid and stigmasterol derivatives. These compounds exhibited significant anti-inflammatory activity through inhibition of **Cyclooxygenase** enzymes, with malabaric acid demonstrating COX-1 inhibitory activity comparable to standard NSAIDs. The isolated compounds also inhibited lipid peroxidation, indicating notable antioxidant potential. By suppressing inflammatory mediators and reducing oxidative damage, *C. viscosa* may also help to protect gastric mucosal tissues against inflammation associated with cellular injury.

d) KUTANNATA[38]- Rodwattanagul S. et. al. (2025) demonstrated that stem bark extracts of *Oroxylum indicum* possess significant **antioxidant, antiglycation, and anti-inflammatory activities** in multiple in vitro models. The extract effectively scavenged free radicals, inhibited the formation of **advanced glycation end-product (AGEs) formation**, and significantly suppressed inflammatory mediators associated with oxidative tissue injury. Phytochemical analysis identified three flavonoids namely, **baicalein, chrysin, and oroxylin A** as well as *p*-coumaric acid as the major bioactive compounds responsible for these effects. Molecular docking studies further revealed a strong interaction of oroxylin A with Toll-like receptor 4 (TLR4), suggesting inhibition of TLR4-mediated inflammatory signaling. Since activation of TLR4 contributes to oxidative stress, NF-κB activation, and chronic inflammation, the observed effects indicate that *O. indicum* may protect against stress-induced cellular damage by attenuating oxidative stress, suppressing inflammatory pathways, and reducing glycation-associated tissue injury.

7) Bio-availability enhancer

a) **PIPPALI[39]-** An in-vivo study by **Shoba G, et al., (1998)** demonstrated the effect of piperine on the bioavailability of curcumin in rats and healthy human volunteers at a dose of 20 mg/kg and 20 mg and 2 g/kg to rats and 2 g respectively. Concomitant administration of piperine increases the t max while elimination half-life and clearance were significantly decreased and the bioavailability was increased by 154%. On the other hand, in humans the increase in bioavailability was 2000%. The study showed that piperine enhances the serum concentration, extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects as such. **Sinha et. al. (2025)** During absorption, piperine does not experience any alterations in metabolism as a result it increases the bioavailability.

8) GAIRIKA[40]

Although, direct pre-clinical studies on Gairika are limited. Traditionally, it has been described as *Dahashamak, Pittaghna, Shothahara,* and *Vishaghna*. **Charde et. al. (2023)** demonstrated that *Shuddha*

Gairika based *Laghusutshekhar Rasa* possesses significant in vitro antacid, prebiotic, and anti-oxidant activities. The study revealed that at 666mg the formulation showed greater antacid activity compared to contemporary medicine gelusil and showed appreciable free-radical scavenging activity in the DPPH assay. It also promoted the growth of beneficial gut microorganisms including *saccharomyces boulardii*, *Lactobacillus paracasei*, *Lactobacillus plantarum*, suggesting a potential role in maintaining healthy gut microbial balance. Its anti-oxidant activity was attributed mainly due to the presence of *shunthi, nagawalli* and other essential minerals. Furthermore, the purification (*Shodhana*) process was reported to improve the physicochemical properties of the formulation, potentially enhancing its bioavailability and therapeutic efficacy. Collectively, these findings indicate that *Gairika*-containing formulations may contribute to gastrointestinal protection, antioxidant defense, and gut homeostasis, which are increasingly recognized as important factors in mitigating stress-related physiological disturbances.

DISCUSSION

Stress contributes to physical and psychological disorders through dysregulation of the HPA axis, oxidative stress, neuroinflammation, neurotransmitter imbalance, and cognitive dysfunction. The findings of this review study suggest that *Dushivishari Agad* possesses multifaceted pharmacological activities, including adaptogenic, neuroprotective, antioxidant, anti-inflammatory, anxiolytic, antidepressant, and gastroprotective effects, which may collectively counteract the pathological mechanisms of chronic stress. Several of its ingredients demonstrated the ability to enhance antioxidant defenses, suppress inflammatory mediators, modulate neurotransmitter systems, and improve cognitive functions, thereby promoting stress resilience and restoration of physiological homeostasis.

From an Ayurvedic viewpoint, chronic stress leads to aggravation of *Manasika Doshas*, particularly *Rajas*, along with *Vata* vitiation, causes *Agnimandya*, and activates *Dushi Visha*, ultimately it affects *Manovaha* and *Rasavaha Srotas*, thereby manifesting as *Chittodvega*. The pharmacological activities observed in the constituent drugs draws close parallel with the Ayurvedic understanding. Antioxidant and anti-inflammatory actions may help reduce the toxic burden of *Dushi Visha* and prevent *Dhatu Dushti*, while *Medhya* and *Rasayana* properties support the restoration of *Dhi, Dhriti*, and *Smriti*, which are often impaired during chronic stress. Modulation of GABAergic and monoaminergic pathways provides a scientific basis for alleviating anxiety, irritability, sleep disturbances, and emotional instability, corresponding to pacification of *Rajas Dosha* and promotion of *Sattva*.

Additionally, maintenance of gastrointestinal health, modulation of the gut microbiota may further contribute to the therapeutic efficacy of the formulation through regulation of the gut-brain axis, reduction in systemic inflammation, and support of neuroendocrine homeostasis. Enhancement of bioavailability through the *Yogavahi* property of *Pippali* may further potentiate the actions of the constituent drugs. Collectively, these actions suggest that *Dushivishari Agad* may reduce the burden of *Dushi Visha*, restore the normal functioning of *Manovaha* and *Rasavaha Srotas*, enhance *Manasika Bala*, and ultimately facilitate *Samprapti Vighatana* in *Chittodvega*.

CONCLUSION

This comprehensive review highlights the therapeutic potential of Dushivishari Agad as a multi-target poly-herbomineral formulation for stress modulation. The available preclinical evidence suggests that its diverse phytoconstituents exert antioxidant, anti-inflammatory, adaptogenic, anxiolytic, nootropic, and neuroprotective effects through multiple pathways involved in the pathophysiology of chronic stress. These findings support the potential role of Dushivishari Agad in enhancing the psychological and physiological resilience. However, direct studies evaluating the formulation as a whole remain limited. Future research should focus on phytochemical standardization, mechanistic investigations, pharmacokinetic profiling, and well-designed clinical trials to establish its efficacy and safety, thereby facilitating its integration into evidence-based stress management strategies.

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