BlissThera®: Harnessing Phytochemical Synergy and Forest Medicine for Comprehensive Homeostasis Support

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Abstract

The physiological advantages of forest exposure are well documented across diverse scientific disciplines. Research indicates that the forest atmosphere contains volatile aerosols emitted by plants, which function as therapeutic agents. BlissThera® is a clinically engineered therapeutic platform that integrates the principles of Forest Medicine with the precision delivery of phytochemicals working in synergy to support multisystemic homeostasis. Utilizing microprocessor-controlled cold diffusion, BlissThera's Bio-Immersive Neuro-Atmosphere Therapy (BINA) administers vapor-phase botanical formulations tailored to specific symptom profiles—optionally paired with immersive virtual nature environments, including electromagnetic geophilic frequencies. This paper examines twelve key physiological systems, ranging from the endocannabinoid and GABAergic networks to the HPA axis and cytokine signaling, and outlines how targeted phytochemical atmospheres can modulate these pathways to restore homeostatic balance. It also presents a cumulative response framework, clinical safety data, and practical models for integration into modern clinical care. BlissThera represents a scalable, non-pharmacologic complementary modality designed to engage the body's innate regulatory architecture through nature-based, technology-assisted therapy.

Scientific Foundations of a Modern Forest Medicine Approach using BlissThera® BINA Therapy Administration

Developed at the intersection of Forest Medicine and clinical phytotherapy, the BlissThera® Bio-Immersive Neuro-Atmosphere Therapy (BINA) platform delivers vapor-phase botanical formulations to support and modulate key homeostatic systems through targeted phytochemical exposure. Inspired by quantitative research on *Shinrin-Yoku* ("forest bathing")[1], the system replicates and amplifies the therapeutic biochemical atmosphere of natural environments within a controlled clinical setting. Studies show that forest environments reduce cortisol levels[2], enhance parasympathetic tone, and stimulate immune function by activating natural killer (NK) cells.[3] These benefits are largely attributed to phytochemicals such as terpenes and phytoncides, volatile organic compounds (VOCs) emitted by trees and plants.[4]

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This inhalation-based exposure to atmospheric phytochemicals, naturally emitted by trees and plants, has been shown not only to improve measurable health markers, but also to correlate with the return of symptoms and inflammatory biomarkers when forest exposure ceases.[5] Moreover, studies indicate that longer durations of exposure result in longer-lasting benefits, suggesting a dose-dependent and transient therapeutic effect. These findings highlight that regular exposure to phytochemical-rich environments is necessary to sustain improvements in physiological health.[6] Importantly, many of these observed outcomes point toward the modulation of underlying homeostatic processes. Homeostasis—the body's dynamic self-regulating balance—is maintained through intricate feedback loops spanning neuroendocrine, immune, vascular, and metabolic systems. The forest atmosphere's diverse spectrum of bioactive compounds appears to interact with these systems in ways that promote recalibration and regulatory stability, establishing a mechanistic basis for the therapeutic effects observed in forest immersion and, by extension, in clinical phytochemical delivery platforms like BlissThera® BINA.

According to the United Nations, in 2014 more than half of the world's population (54%) lived in urban environments. This is projected to increase to 66% by 2050.[7] Urban environments have been demonstrated to contain a lower diversity and concentration of beneficial volatile organic compounds (VOC) like ß-myrcene, D-limonene, caryophyllene, α-farnesene, alpha-cuparene, as well as a greater number and higher concentrations of harmful VOCs such as benzene, toluene, ethylbenzene, and styrene.[8] An association between urban living and an increased prevalence of certain diseases (e.g. autoimmune disorders, diabetes, cancer, mental health disorders) suggests these to be *Urban-Associated Diseases* for which many potential causes may be considered.[9]

Taken together, these patterns point toward a unifying hypothesis: that chronic underexposure to atmospheric phytochemicals in urbanized environments may represent a distinct clinical phenomenon—supported by evidence of increased disease prevalence, diminished health outcomes in urban populations, the transient nature of Shinrin-Yoku's therapeutic effects, and the stark contrast in phytochemical content between forest and city air. Observational data from patients undergoing BlissThera® BINA therapy further reinforce this pattern: symptomatic improvement occurs with regular exposure to phytochemical atmospheres, but often recedes when therapy is paused.[10] These clinical outcomes mirror the transient benefits of forest immersion and suggest a dose-dependent, reversible biological response, wherein sustained improvement requires continued exposure.

This emerging framework forms the basis for what may be termed a ***Clinical Phytochemical Deficiency (CPD).*** Historically, human populations lived immersed in natural environments, continuously inhaling low levels of botanical VOCs that may have acted as substrates for physiological regulation. These compounds—such as terpenes, phenolics, and other plant-emitted VOCs—likely served as modulators of immune activity, stress resilience,

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[10] BlissThera Clinical Case Reports

and systemic homeostasis. In contrast, modern life—characterized by deforestation, urban air pollution, ultra-processed food diets, and prolonged artificial indoor confinement—has dramatically reduced exposure to these environmental bioactive inputs. As a result, individuals may operate in a chronically deficient state, lacking the ambient biochemical cues necessary to maintain optimal regulatory function. ***The CPD hypothesis*** offers a compelling lens through which to interpret both the widespread dysregulation observed in chronic illness and the therapeutic improvements seen with reintroduction of phytochemical atmospheres via BINA therapy.[11]

BlissThera's BINA therapy addresses this imbalance by reintroducing a curated spectrum of phytochemicals shown to modulate key physiological pathways through a microprocessor-controlled cold diffusion system that delivers condition-specific vapor-phase formulations into the ambient clinical environment. These formulations—comprising volatile terpenes and other inhalable botanical compounds—are stored in modular cartridges and released via precision-timed diffusion cycles governed by proprietary software algorithms. The dosing profile, duration, and composition of each session are adjustable and informed by clinical data, symptom severity, and patient response. This vapor-phase delivery model enables high bioavailability and rapid uptake through the respiratory tract[12] without combustion, heating, or invasive administration. Optional integration with immersive audiovisual nature simulation and electromagnetic geophilic frequencies further enhances parasympathetic activation and supports sensory coherence during therapy.[13,14]

Clinic Generated Forest Atmosphere Delivery

Inhaled atmosphere delivery offers several distinct advantages over conventional administration routes such as oral ingestion, injection, or transdermal absorption. The pulmonary route provides a large surface area and the lipophylic nature of phytochemicals provide ready access to pulmonary vasculature, allowing therapeutic compounds to be rapidly absorbed into circulation, thus achieving a faster onset of action as well as avoiding extensive first-pass hepatic metabolism. This is particularly valuable when targeting neurochemical pathways, as some volatile phytochemicals interact with the olfactory epithelium to produce effects.[15] Bioavailability of inhaled phytochemicals is significantly higher by inhalation (50-70%) compared to oral administration (3-10%).[16] Additionally, vapor-phase administration enables non-invasive, easily titratable dosing that can be easily modulated in real time based on patient response. Unlike pills or injections, inhaled delivery engages multiple sensory systems, including olfactory and autonomic pathways, which may enhance limbic and parasympathetic effects, contributing to both physiological regulation and subjective

[11] BlissThera Clinical Case Reports

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therapeutic experience.[17,18] For patients with polypharmacy concerns, gastrointestinal sensitivity, or needle aversion, the inhaled modality offers a well tolerated, safer, gentler, and more accessible route.

Vortex-Generated Vapor Atmosphere

Research on natural forest and waterfall environments has demonstrated measurable health effects associated with their unique aerosol profiles, including reduced inflammatory signaling—such as downregulation of NF-κB in lung tissue—and enhanced mucosal immunity, including increased salivary IgA levels.[19] Studies in both humans and animal models further associate negatively charged air ions[20], commonly found near waterfalls and dense forest air, with reduced anxiety, mood improvement, and improved immune regulation.[21] These findings suggest that the physical properties of airborne particles and their delivery dynamics (with or without phytochemicals) play a significant role in therapeutic outcomes.

BlissThera's BINA therapy incorporates these principles through a patented vortex diffusion system that generates a cyclonic airflow pattern, producing fine mist dispersion that mimics the micro-aerosols of natural environments. This vortex-generated vapor atmosphere improves pulmonary deposition and olfactory engagement compared to conventional static nebulization techniques, allowing for more consistent and higher bioavailability of inhaled phytochemicals.[22,23]

Homeostatic Systems and Phytochemical Modulation

Homeostasis depends on coordinated signaling across multiple feedback loops that maintain internal equilibrium in response to external challenges. This balance is regulated by a complex network of neural pathways, neurotransmitters, endocrine axes, immune mediators, and vascular signaling molecules—all of which must dynamically adapt to shifting physiological demands.[24] The following sections outline how BlissThera's BINA Therapy precisely engineered phyto-atmospheres engage twelve key physiological systems that play central roles in maintaining homeostasis. For each system, its regulatory function is described alongside evidence of phytochemical modulation, emphasizing human clinical findings and supported by relevant animal and in vitro data.

These twelve systems include the endocannabinoid, GABAergic, glutamatergic, dopaminergic, serotonergic, cholinergic, adrenergic, and opioidergic networks; the renin–angiotensin–aldosterone system (RAAS); the hypothalamic–pituitary–adrenal (HPA) axis; nitric oxide (NO) signaling pathways; and cytokine regulatory networks. Each is examined through the lens of its molecular mechanisms, receptor pathways, and known phytochemical modulators—providing clinicians with a structured framework for understanding how targeted

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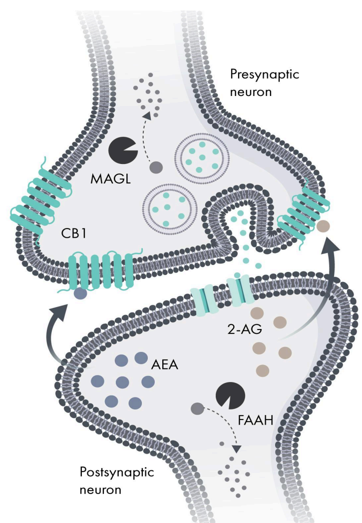
vapor-phase botanical therapies may support systemic regulation, resilience, and recovery across a wide range of chronic conditions.

1. Endocannabinoid System (ECS)

Physiological Function: The ECS is a lipid signaling network governing neuroimmune communication, pain sensation, appetite, mood, inflammation, and stress resilience. It comprises cannabinoid receptors (CB) present throughout all body tissues (CB_1 primarily in the central nervous system, CB_2 in peripheral and immune tissues), their endogenous ligands (anandamide, 2-AG), and metabolic enzymes (FAAH, MAGL) that degrade these ligands.[25] Functioning as a retrograde signaling mechanism, endocannabinoids are produced by postsynaptic neurons in response to excessive receptor activation, crossing the synapse and binding to presynaptic CB_1/CB_2 receptors to inhibit additional neurotransmitter release and maintain homeostasis. This system thus maintains balance in pain perception, metabolic processes, CNS arousal, inflammation, and emotional reactivity.[26]

Phytochemical Modulation: Several terpenoid phytochemicals can enhance or mimic endocannabinoid activity. β-Caryophyllene, a sesquiterpene found in many spices, is a selective CB_2 agonist that binds directly to CB_2 receptors, producing cannabimimetic effects without psychoactivity. In animal models, β-caryophyllene's activation of CB_2 has been shown to reduce neuroinflammation, alleviate inflammatory and neuropathic pain, and lower anxiety-like behaviors.[27] Other terpenes such as limonene, α-pinene, and myrcene may indirectly boost ECS tone.[28] Preclinical research suggests these terpenes inhibit FAAH (the enzyme that degrades anandamide), thereby prolonging anandamide signaling and enhancing endocannabinoid receptor activation. Early human evidence comes from trials of broad-spectrum hemp extracts rich in CBD, also a FAAH inhibitor[29], and terpenes: in chronic pain and anxiety patients, such extracts showed greater efficacy than CBD isolate, pointing toward an "entourage effect" where terpenes synergize with cannabinoids.[30] (Notably, direct clinical trials isolating terpenes for ECS effects are still limited.) Overall, these phytochemicals support ECS function by activating cannabinoid receptors or modulating the body's own endocannabinoid signals, contributing to pain relief, anti-inflammatory effects, and stress adaptation.



Simplified schematic representation of endocannabinoid signaling. Endocannabinoids act on presynaptic CB1 receptors (primarily located in the CNS) and CB2 receptors (prevalent in the periphery and in immune cells), modulating neurotransmitter

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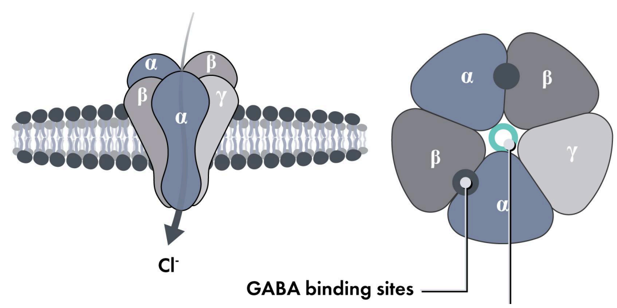
release, regulating physiologic and immune responses. Endocannabinoids are inactivated and degraded by the monoacylglycerol lipase (MAGL) in the case of 2-AG, and fatty acid amide hydrolase (FAAH) for AEA.

2. GABAergic System

Physiological Function: The GABAergic system is the body's primary inhibitory network in the brain and spinal cord. Gamma-aminobutyric acid (GABA) acting on GABA_A (ionotropic) and GABA_B (metabotropic) receptors induces neuronal hyperpolarization, which stabilizes neural circuits and prevents over-excitation. This inhibition is crucial for controlling anxiety, promoting sleep, preventing seizures, and modulating pain signals. Proper GABA activity produces calm and relaxation, whereas deficiencies in the GABA system can result in anxiety disorders, insomnia, epilepsy, and chronic pain due to unchecked neural firing.[31]

Phytochemical Modulation: Several aromatherapeutic terpenes positively modulate GABA receptors to enhance inhibitory tone. Linalool, a monoterpene alcohol abundant in lavender, is a well-known GABAergic modulator. In preclinical studies, inhaled linalool interacts with GABA_A receptor sites and potentiates GABA's effects, leading to significant anxiolytic and sedative outcomes.[32] Human trials with oral lavender oil (rich in linalool) have borne this out: a 6-week clinical trial found a linalool-containing supplement (*Silexan*) as effective as a benzodiazepine in alleviating generalized anxiety, without sedative side effects.[33] β-Myrcene, found in hops and lemongrass, also exhibits sedative and muscle-relaxant properties through GABAergic pathways.[34] Rodent studies demonstrate myrcene increases sleeping time and impairs motor coordination at high doses, effects akin to tranquilizers.[35] Borneol, a bicyclic terpene (from valerian and other herbs), has been shown in vitro to be a positive allosteric modulator of GABA_A receptors. Pharmacological studies demonstrate that borneol dramatically enhances GABA_A currents, by over 1000% at certain concentrations, without binding to benzodiazepine sites.[36] This GABA-potentiating action of borneol underlies its traditional use as a calmative agent. Together, these phytochemicals (often inhaled as essential oils or taken as herbal extracts) increase GABAergic inhibition, yielding anti-anxiety, anticonvulsant, and sedative benefits. Importantly, human data is strongest for lavender/linalool (anxiolysis and improved sleep in clinical use)[37], while others like myrcene and borneol are supported by animal or ex vivo evidence.



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Simplified schematic representation of the GABA-A receptor. Activation of the GABA-A receptor results in more frequent opening of the chloride ion channel producing hyperpolarization, inhibiting activity of the system.

3. Glutamatergic System

Physiological Function: Glutamate is the primary excitatory neurotransmitter in the central nervous system, crucial for synaptic plasticity, learning, memory formation, and overall cortical activity. It activates ionotropic receptors (NMDA, AMPA, kainate) to depolarize neurons and metabotropic glutamate receptors for neuromodulation. Under normal conditions, glutamatergic transmission drives cognition and motor function. However, excessive glutamate release or NMDA receptor overactivation leads to excitotoxicity, damaging or killing neurons via calcium overload. Thus, the glutamatergic system must maintain a delicate balance: enough activity for plasticity and memory, but restrained to avoid seizures, neurodegeneration, or cell death after ischemic injuries.[38]

Phytochemical Modulation: Certain plant terpenes exhibit neuroprotective effects by tempering glutamate-driven excitotoxicity. α-Pinene, a monoterpene from conifer resins, has demonstrated NMDA-receptor modulating properties. In rodent models of ischemic stroke, α-pinene administration reduced the extent of neuronal damage and improved neurological outcomes. Its benefits are attributed to anti-inflammatory and possibly NMDA-antagonist actions, which attenuate the harmful calcium influx during ischemia.[39] Similarly, nerolidol (a sesquiterpene alcohol in citrus and lavender)[40] and linalool have shown neuroprotective effects in cellular models of glutamate toxicity.[41] In vitro studies on cultured neurons report that pretreatment with linalool mitigates glutamate-induced oxidative stress and cell death, likely by enhancing antioxidant defenses and suppressing inflammatory mediators.[42] While direct human research is lacking for this pathway, these terpenes' ability to cross the blood–brain barrier and shield neurons is promising.[43] Traditional aromatherapy using terpene-rich essential oils (e.g. rosemary, high in pinene and eucalyptol) is historically associated with cognitive clarity and calming effects.[44] In summary, by modulating NMDA receptor activity, reducing glutamate release, or counteracting downstream oxidative damage, phytochemicals like α-pinene, nerolidol, and linalool help protect the brain from overstimulation and support healthy cognitive function.

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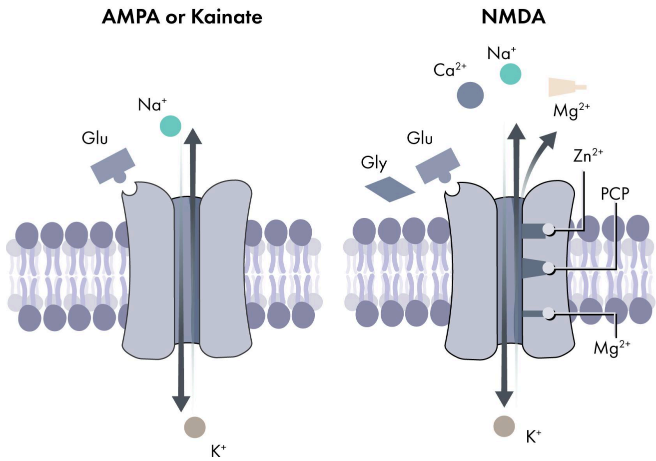

Simplified schematic representation of NMDA receptor signaling. Once activated NMDA receptors allow the influx of Ca^{2+} and Na^{+}, and efflux of K^{+}. Depolarization via NMDA receptor-mediated currents contributes to excitatory postsynaptic potentials (EPSPs).

4. Dopaminergic System

Physiological Function: The dopaminergic system regulates reward, motivation, pleasure, attention, motor control, and executive function. Dopamine neurons in midbrain regions project to key areas: the mesolimbic pathway (ventral tegmental area to nucleus accumbens) mediates reward and reinforcement learning; the mesocortical pathway (VTA to prefrontal cortex) influences cognition and mood; and the nigrostriatal pathway (substantia nigra to striatum) controls voluntary movement. Dopamine D1–D5 receptors modulate neuronal excitability in these circuits. Balanced dopamine signaling is essential: too little dopamine (as in Parkinson's disease) causes motor rigidity and apathy, while dysregulated dopamine (as in addiction or schizophrenia) disrupts behavior and reality testing. Optimal dopamine tone supports focus, drive, emotional wellbeing, and coordinated movement.[45]

Phytochemical Modulation: Certain uplifting essential oils contain terpenes that interact with dopaminergic pathways. d-Limonene, the dominant terpene in citrus peel, has been shown to influence brain dopamine levels.[46] Inhalation of lemon oil vapor in mice produced antidepressant-like effects and significantly accelerated the metabolic turnover of DA in the hippocampus.[47] This aligns with human aromatherapy findings: citrus fragrance exposure tends to improve mood and may reduce depressive symptoms, partly via modulating monoamine (including dopamine) activity.[48] Another compound, eugenol (a phenolic terpene in clove oil), impacts dopamine by inhibiting its breakdown. Eugenol is a reversible MAO-A inhibitor, as shown in vitro by its low micromolar inhibition of monoamine oxidase. By slowing dopamine's enzymatic degradation, eugenol can prolong dopamine's action in the synapse.[49] Indeed, in animal models, eugenol demonstrated antidepressant-like effects comparable to standard antidepressants, an effect attributed to its MAO-inhibitory, dopamine-sparing activity.[50] Additionally, β-Pinene (from pine resin and many herbs) appears to support dopamine-mediated cognitive functions. Preclinical studies indicate β-pinene has pro-cognitive and antidepressant effects, possibly by enhancing dopaminergic

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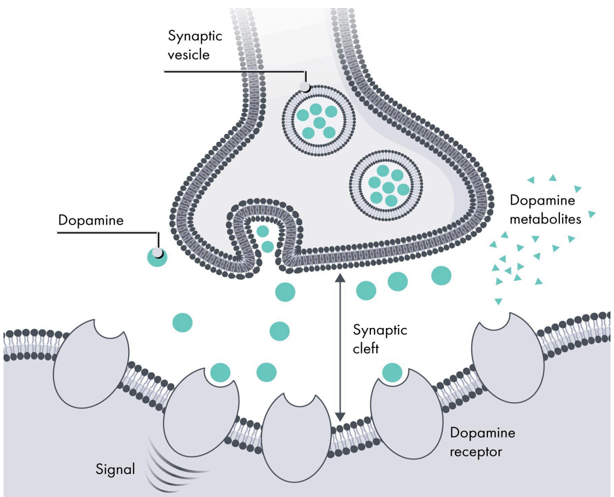
[49] Berlowitz, I., Egger, K., & Cumming, P. (2022). Monoamine Oxidase Inhibition by Plant-Derived β-Carbolines; Implications for the Psychopharmacology of Tobacco and Ayahuasca. *Frontiers in Pharmacology*, *13*, 886408.

[50] do Amaral JF, Silva MI, de Aquino Neto MR, Moura BA, de Carvalho AM, Vasconcelos PF, Barbosa Filho JM, Gutierrez SJ, Vasconcelos SM, Macêdo DS, de Sousa FC. Antidepressant-like effect of bis-eugenol in the mice forced swimming test: evidence for the involvement of the monoaminergic system. Fundam Clin Pharmacol. 2013 Oct;27(5):471-82. doi: 10.1111/j.1472-8206.2012.01058.x. Epub 2012 Jul 25. PMID: 22827775.

transmission in the prefrontal cortex.[51] For example, β-pinene showed neuroprotective effects in models of Alzheimer's, reducing oxidative damage and consequently improving memory and learning performance.[52] Rodent experiments also suggest β-pinene can improve working memory and attention, consistent with traditional claims that pine aroma clears the mind.[53] Together, these phytochemicals boost dopaminergic signaling either by increasing dopamine levels (limonene's effect on synthesis/release), inhibiting dopamine metabolism (eugenol's MAO inhibition), or protecting dopamine neurons (β-pinene's antioxidant neuroprotection). Clinically, this translates to potential mood enhancement, stress relief, and cognitive sharpening – effects observed anecdotally with citrus and spice oils and increasingly supported by scientific study.[54]



Simplified schematic representation of dopamine receptor signaling. Binding of dopamine to the dopamine receptor causes an intracellular signaling cascade (involving adenyl cyclase, G-proteins, Ca^{2+}, phospholipase C, others) which triggers downstream effects.

5. Serotonergic System

Physiological Function: The serotonergic system, centered on the neurotransmitter serotonin (5-HT), modulates mood, anxiety, appetite, sleep-wake cycles, and gastrointestinal motility. Serotonin-producing neurons in the raphe nuclei of the brainstem project widely throughout the brain and down the spinal cord. Through various receptors ($5\text{-}HT_1$–$5\text{-}HT_7$ subtypes), serotonin influences emotional balance, stress response, and cognitive flexibility. For instance, $5\text{-}HT_1A$ receptors mediate anxiolysis and mood stabilization, while $5\text{-}HT_2$ receptors affect perception and impulse control. Adequate serotonin levels and receptor function are linked to feelings of well-being and calm; conversely, serotonin deficiencies or receptor dysfunction manifest in depression, anxiety disorders, disrupted sleep, and altered appetite. The gut-brain axis is also largely serotonergic, as the majority of the body's serotonin resides in the GI tract regulating digestion and communicating with the brain.[55]

Phytochemical Modulation: Phytochemicals can interact with the serotonergic system to promote a positive mood and stress resilience. Cannabidinol (CBD) acts as a partial agonist at the $5\text{-}HT_1A$ receptor, a subtype of serotonin receptor involved in anxiety, mood, and stress regulation.[56] Linalool (from lavender) not only engages GABAergic

[51] Weston-Green, K., Clunas, H., & Jimenez Naranjo, C. (2021). A Review of the Potential Use of Pinene and Linalool as Terpene-Based Medicines for Brain Health: Discovering Novel Therapeutics in the Flavours and Fragrances of Cannabis. *Frontiers in Psychiatry*, *12*, 583211.
[52] Dahiya M, Kumar A, Yadav M, Chauhan S. β-pinene ameliorates ICV-STZ induced Alzheimer's pathology via antioxidant, anticholinesterase, and mitochondrial protective effects: In-silico and in-vivo studies. Eur J Pharmacol. 2025 Mar 15;991:177307. doi: 10.1016/j.ejphar.2025.177307. Epub 2025 Jan 25. PMID: 39870228.
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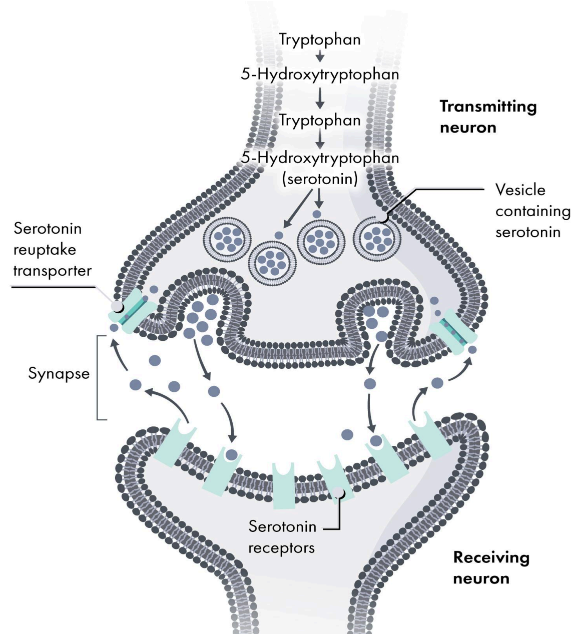
[56] Mendiguren A, Aostri E, Alberdi E, Pérez-Samartín A and Pineda J (2022), Functional characterization of cannabidiol effect on the serotonergic neurons of the dorsal raphe nucleus in rat brain slices. Front. Pharmacol. 13:956886.

pathways but also has an affinity for serotonin receptors. Animal research suggests linalool may bind to 5-HT₁A receptors or downstream signaling, contributing to its anti-anxiety effects. In human trials, lavender oil's efficacy for anxiety (as noted earlier) is partly attributed to serotonergic modulation in limbic brain regions.[57] Another terpene, β-Pinene, has been observed to influence serotonin levels. Studies in mice have found that exposure to pinene-rich essential oils produces antidepressant-like outcomes, correlating with increased serotonin turnover in the brain.[58] This aligns with traditional use of pine and rosemary aromas for mental clarity and uplifted mood. Terpinen-4-ol, a component of tea tree and marjoram oils, shows promise as well. In a mouse model of depression, terpinen-4-ol–rich marjoram oil significantly improved depressive behaviors, with evidence that it raised brain serotonin and noradrenaline levels. This terpene likely exerts its effect by enhancing monoamine neurotransmission and reducing HPA-axis hyperactivity associated with stress.[59] Cumulatively, these findings illustrate that phytochemicals can enhance serotonergic signaling through various mechanisms – receptor binding, slowing serotonin breakdown, or stimulating its release. Clinically, inhalation or ingestion of such terpene-rich oils has been reported to improve mood, reduce anxiety, and even aid sleep (since serotonin is a precursor to melatonin). While human data are most robust for lavender (with multiple RCTs supporting anxiolytic and antidepressant effects), the converging animal data on pinene and terpinen-4-ol support their historical use as mood modulators via the serotonin system.



Simplified schematic representation of serotonin receptor signaling. The binding of serotonin to a serotonin receptor (mostly of the G protein-coupled family) activates an intracellular signaling cascade involving ion channels, adenyl cyclase, phospholipase C producing excitatory or inhibitory responses, depending on neural pathways affected.

6. Cholinergic System

Physiological Function: The cholinergic system relies on the neurotransmitter acetylcholine (ACh) and is vital for attention, learning, memory formation, and neuromuscular control. In the central nervous system, cholinergic neurons (for example, from the basal forebrain) project to the cortex and hippocampus, modulating arousal and encoding of memories. In the peripheral nervous system, ACh released at neuromuscular junctions triggers muscle contraction, and in the autonomic nervous system ACh transmits parasympathetic signals ("rest and digest"). ACh acts on nicotinic receptors located at the neuromuscular junction and autonomic ganglia through modulation of ion channels, and on muscarinic receptors present on target organs (glands, smooth muscle, cardiac muscle, central nervous system) through

[57] dos Santos, É. R. Q., Maia, J. G. S., Fontes-Júnior, E. A., & Maia, C. S. F. (2022). Linalool as a Therapeutic and Medicinal Tool in Depression Treatment: A Review. *Current Neuropharmacology*, *20*, 1073–1092.
[58] Weston-Green, K., Clunas, H., & Jimenez Naranjo, C. (2021). A Review of the Potential Use of Pinene and Linalool as Terpene-Based Medicines for Brain Health: Discovering Novel Therapeutics in the Flavours and Fragrances of Cannabis. *Frontiers in Psychiatry*, *12*, 583211.
[59] Vieira, G., Cavalli, J., Gonçalves, E. C. D., Braga, S. F. P., Ferreira, R. S., Santos, A. R. S., Cola, M., Raposo, N. R. B., Capasso, R., & Dutra, R. C. (2020). Antidepressant-Like Effect of Terpineol in an Inflammatory Model of Depression: Involvement of the Cannabinoid System and D2 Dopamine Receptor. *Biomolecules*, *10*(5), 800. doi: 10.3390/biomolecules10050800

G-protein coupled mechanisms, to exert its effects. Proper cholinergic transmission supports alertness, quick information processing, and muscle coordination. Impairment in this system, such as loss of cholinergic neurons in Alzheimer's disease, leads to memory deficits and confusion, while blocking peripheral ACh (by anticholinergic drugs) causes dry mouth, constipation, and elevated heart rate. Thus, enhancing cholinergic function can improve cognition and focus, whereas dampening it can have sedative or adverse cognitive effects.[60]

Phytochemical Modulation: A number of plant-derived compounds can boost cholinergic activity by inhibiting acetylcholinesterase (AChE) or otherwise enhancing ACh signaling. 1,8-Cineole (eucalyptol), a major component of eucalyptus and rosemary oils, has demonstrated pro-cholinergic cognitive benefits. The mechanism is thought to be cineole's mild inhibition of AChE, resulting in more acetylcholine available in synapses.[61] Pinene decreases acetylcholinesterase activity, and affects proteins involved in acetylcholine synthesis to increase levels, resulting in improved memory and cognitive function.[62] α-Terpineol, a monoterpene alcohol found in pine oil and citrus, has shown neuroprotective effects on cholinergic neurons in animal studies. For example, in a rat model of stroke, α-terpineol treatment improved cognitive recovery and increased markers of synaptic plasticity in the hippocampus (indicative of cholinergic circuit preservation). It likely acts by reducing oxidative damage and inflammation post-ischemia, thereby helping ACh neurons survive and function.[63] Borneol, mentioned earlier for GABA, also benefits the cholinergic system, particularly in the context of drug delivery and neuroprotection. It is known to facilitate drug penetration into the brain (crossing the blood–brain barrier) and has been used in Chinese medicine to enhance the effects of other cognition-enhancing herbs.[64] In models of Alzheimer-like injury, borneol co-administered with cholinergic drugs led to greater restoration of ACh levels and improved memory than the drugs alone. Moreover, borneol itself may exert mild anti-AChE activity and anti-inflammatory action in the brain, thereby indirectly protecting cholinergic neurons.[65] The net effect of these phytochemicals is improved cholinergic transmission: human subjects have reported heightened focus and clarity with rosemary oil inhalation,[66] and animal models demonstrate preserved or enhanced memory performance with compounds like terpineol and borneol. These findings underscore the potential of terpene-based interventions in supporting cognitive function and even slowing cholinergic deficits in neurodegenerative conditions.

[60] Tiwari, P., Dwivedi, S., Singh, M. P., Mishra, R., & Chandy, A. (2013). Basic and modern concepts on cholinergic receptor: A review. *Asian Pacific Journal of Tropical Disease*, *3*(5), 413–420. doi: 10.1016/S2222-1808(13)60094-8

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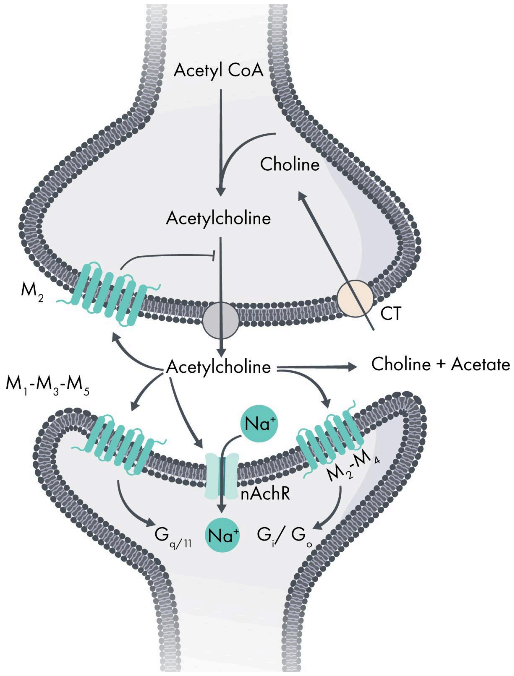

Simplified schematic representation of acetylcholine receptor signaling. Binding of ACh to nicotinic ACh receptors causes membrane ion channels to open (Ca^{2+}, Na^{+}, K^{+}) causing nerve depolarization. Binding of ACh to muscarinic ACh receptors results in a cascade of intracellular signaling (involving G proteins) leading to a variety of effects including modulation of enzyme activity or gene expression.

7. Adrenergic System

Physiological Function: The adrenergic system drives the "fight-or-flight" response through the neurotransmitters norepinephrine (noradrenaline) and epinephrine (adrenaline) acting on α- and β-adrenergic receptors. Sympathetic nerve activation releases norepinephrine increasing heart rate and contractility, induces vasoconstriction of blood vessels increasing peripheral resistance and blood pressure, and causes bronchodilation, among other organ system effects. Adrenergic stimulation prepares the body to respond to stress by enhancing blood flow to muscles, raising blood glucose, and sharpening attention. However, chronic overactivation of this system contributes to hypertension, anxiety (hypervigilance), insomnia, and metabolic strain.[67] A balanced adrenergic tone is needed, enough to maintain blood pressure and respond to acute stress, but low during rest to allow recovery and digestion (mediated by the parasympathetic system).[68]

Phytochemical Modulation: Certain soothing plant volatiles can reduce excessive sympathetic activity and support parasympathetic (calming) tone. Linalool, from lavender, exemplifies this effect. In animal studies and human experiments, linalool-rich aromas produce measurable decreases in heart rate and blood pressure, lower anxiety and stress hormone levels, indicative of reduced adrenergic output and increased vagal (parasympathetic) tone.[69] β-Caryophyllene indirectly modulates adrenergic function by dampening stress-related inflammation and anxiety via CB_2 activation[70], thereby preventing secondary sympathetic surges under chronic stress. Cannabingerinol (CBG) is also a CB_2 ligand, and is a highly potent alpha$_2$-adrenoceptor agonist, producing a decrease in sympathetic nervous system tone.[71] This results in a relatively higher parasympathetic state as reflected by lower blood pressure, heart rate, as well as producing anxiolytic and analgesic effects. 1,8-Cineole (Eucalyptol) offers another angle: it has mild bronchodilatory effects (useful for respiratory function) without significantly raising heart rate or blood pressure. In fact, clinical studies in airway disease patients found that

[67] Graham, R. M. (1990). Adrenergic receptors: structure and function. *Cleveland Clinic Journal of Medicine*, *57*(5), 481–491.
[68] Buijs RM. The autonomic nervous system: a balancing act. Handb Clin Neurol. 2013;117:1-11. doi: 10.1016/B978-0-444-53491-0.00001-8. PMID: 24095111.
[69] dos Santos, É. R. Q., Maia, J. G. S., Fontes-Júnior, E. A., & Maia, C. S. F. (2022). Linalool as a Therapeutic and Medicinal Tool in Depression Treatment: A Review. *Current Neuropharmacology*, *20*, 1073–1092.
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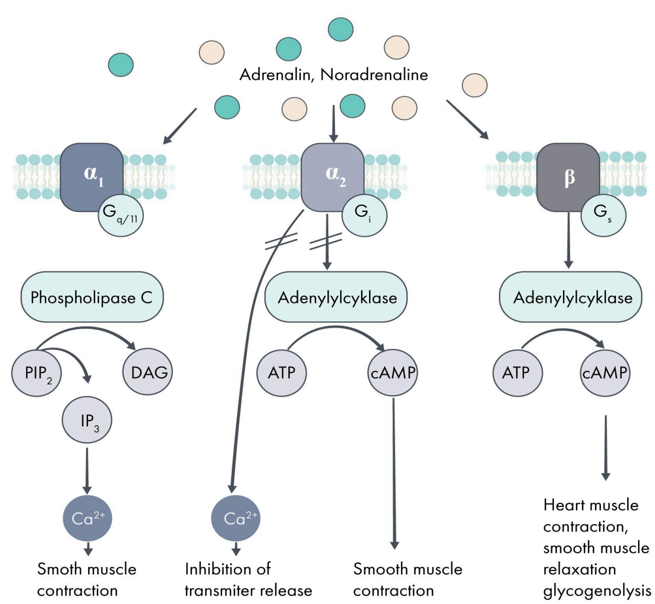
eucalyptol improved breathing and had an anti-inflammatory effect on airways, which resulted in significant decreases in the frequency, duration, and severity of COPD exacerbations.[72] Eucalyptol's refreshing scent can also enhance alertness and mood, potentially via modest stimulation of β-adrenergic receptors in the brain[73], but notably without the jitteriness associated with caffeine or other stimulants. Together, these phytochemicals help balance the adrenergic system: linalool predominantly calms an overactive sympathetic response (lowering blood pressure, heart rate, and perceived stress), β-caryophyllene and CBG aid in blunting chronic stress signals (preventing adrenergic overdrive), and eucalyptol supports respiratory and cognitive function in a controlled manner. The net clinical outcome is a more favorable autonomic profile – a lower resting heart rate and blood pressure, improved stress coping, which is beneficial in hypertension, anxiety, and stress-related disorders.



Simplified schematic representation of adrenergic receptor signaling. Activation of the $\boldsymbol{\alpha_1}$ *receptor causes smooth muscle contraction; activation of* $\boldsymbol{\alpha_2}$ *receptor causes smooth muscle contraction, and decreases adrenergic neurotransmitter release which decreases sympathetic tone; activation of the* $\boldsymbol{\beta}$ *receptor causes increased cardiac muscle contraction, smooth muscle relaxation and glycogenolysis.*

[72] Hoch, C. C., Petry, J., Griesbaum, L., Weiser, T., Werner, K., Ploch, M., Verschoor, A., Multhoff, G., Dezfouli, A. B., & Wollenberg, B. (2023). 1,8-cineole (eucalyptol): A versatile phytochemical with therapeutic applications across multiple diseases. *Biomedicine & Pharmacotherapy*, *167*, 115467.
[73] Goto, S., Suzuki, H., Nakagawa, T., & Shimizu, K. (2020). The Effect of Eucalyptol on Nursing Home Residents. *Scientific Reports*, *10*(1), 3996.

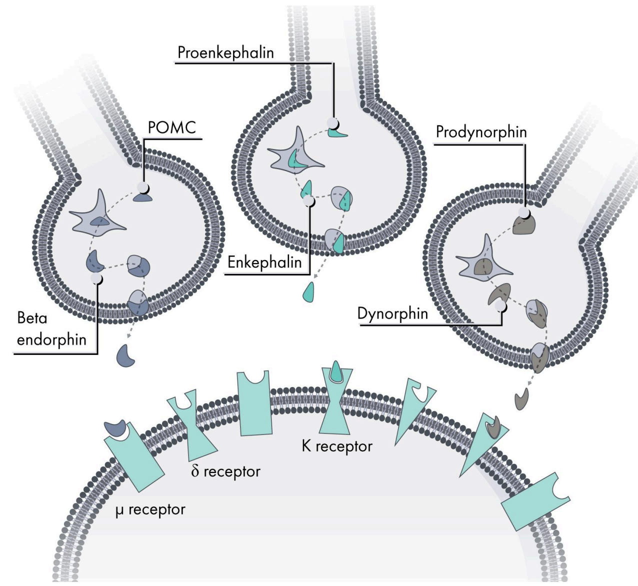
8. Opioidergic System

Physiological Function: The opioidergic system involves endogenous opioids (endorphins, enkephalins, dynorphins) and their receptors (mu, delta, kappa) which regulate pain perception, reward, stress responses, and social bonding. When activated (e.g. by endorphins binding mu-opioid receptors), this system produces analgesia, euphoria, and a sense of well-being. It is a primary pathway for pain relief mediated by both natural endogenous opioids and opioid pharmaceuticals. Proper functioning helps the body tolerate pain and stress, and reinforces positive behaviors (via dopamine interactions in reward centers). Dysregulation of the opioid system is seen in chronic pain (when endogenous opioids are insufficient), in opioid addiction (the drugs hijack the reward pathway), and in mood disorders (since opioids modulate mood and anxiety). Supporting proper endogenous opioid release and receptor balance can thus improve pain control and emotional resilience.[74]

Phytochemical Modulation: Certain terpenes can influence the opioid system, often by indirectly boosting the body's own opioid-mediated analgesia. β-Caryophyllene (BCP), beyond its direct CB_2 agonism, has been shown to produce significant pain relief in animal models through influencing cross-talk with opioid pathways. Research indicates that BCP's analgesic effect is partly reversed by naloxone (an opioid antagonist), suggesting BCP triggers the release of endorphins or otherwise engages opioid receptors secondarily. In inflammatory pain models, oral β-caryophyllene reduced pain

[74] Chaudhry, S. R., & Gossman, W. (2023, April 3). *Biochemistry, Endorphin*. National Center for Biotechnology Information.

behaviors comparably to NSAIDs, and combined CB_2/opioid blockade was needed to fully negate its analgesia, highlighting a synergistic cannabinoid-opioid mechanism.[75] Myrcene also exhibits opioid-like analgesic properties. Classic studies on myrcene found it has a potent antinociceptive effect in mice, raising pain thresholds. Notably, this analgesia was blocked by naloxone, implicating activation of endogenous opioid pathways. Myrcene's sedative effects likely contribute by reducing pain perception and anxiety, but the naloxone finding means myrcene likely causes the body to release more endorphins or makes mu-opioid receptors more responsive. Limonene, while known for mood elevation, may also play a supportive role in pain modulation. Animal studies of limonene demonstrate not only anxiolytic and antidepressant effects but also reduced pain behaviors in models of neuropathic and inflammatory pain. Its pain-relieving action is modest alone, but limonene seems to enhance the analgesic effect of conventional opioids when used together, a potential entourage effect noted in cannabis research.[76, 77] In human contexts, full-spectrum CBD oils containing trepenes have been reported to yield better pain relief than isolated molecular CBD, again hinting at opioid system interplay.[78] In summary, terpenes like β-caryophyllene and myrcene augment endogenous opioid signaling, by promoting endorphin release or increasing receptor activation, thereby contributing to natural analgesia and stress relief. Clinically, this can translate to reduced pain sensation, improved tolerance for chronic pain, and possibly lower required doses of concurrently prescribed opioid medications, offering a safer and more effective approach to pain management.



Simplified schematic representation of opioidergic receptor signaling. The endogenous opioid system operates via peptides like β-endorphin, enkephalin, or dynorphin binding to specific G protein-coupled receptors (μ, δ, and κ) with selectivity leading to varied signaling cascades and physiological effects.

9. Renin–Angiotensin–Aldosterone System (RAAS)

Physiological Function: The RAAS is a hormone system that regulates blood pressure, fluid balance, and electrolyte levels. When renal blood flow is low, the kidneys release renin, which converts angiotensinogen (from the liver) to angiotensin I; this is then converted by ACE (angiotensin-converting enzyme) to angiotensin II, a potent vasoconstrictor. Angiotensin II raises blood pressure by narrowing blood vessels and stimulating the adrenal cortex to release aldosterone, which causes the kidneys to retain sodium and water, increasing blood volume. RAAS activation thus helps in maintaining blood pressure and vascular volume, but chronic overactivation leads to hypertension, edema,

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[75] Francomano, F.; Caruso, A.; Barbarossa, A.; Fazio, A.; La Torre, C.; Ceramella, J.; Mallamaci, R.; Saturnino, C.; Iacopetta, D.; Sinicropi, M.S. β-Caryophyllene: A Sesquiterpene with Countless Biological Properties. *Appl. Sci.* 2019, *9*, 5420.

[76] Alfieri, A.; Di Franco, S.; Maffei, V.; Sansone, P.; Pace, M.C.; Passavanti, M.B.; Fiore, M. Phytochemical Modulators of Nociception: A Review of Cannabis Terpenes in Chronic Pain Syndromes. *Pharmaceuticals* 2025, *18*, 1100.

[77] Fakhri, S., Yarmohammadi, M., Abbaszadeh, F., Kiani, A., & Farzaei, M. H. (2025). Unveiling the anti-inflammatory and antinociceptive effects of limonene in two models of carrageenan-induced inflammation and formalin-induced pain: role of l -arginine/nitric oxide/cGMP/K ATP channel signaling pathways, opioidergic, and benzodiazepine receptors. *Behav Pharmacol*, *36*(6), 378–386.

[78] Gallily, R., Yekhtin, Z., & Hanuš, L. O. (2015). Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol. *Pharmacology & Pharmacy*, *6*(2), 75–85.

arterial stiffness, and organ damage. Components of RAAS such as angiotensin II (via AT_1 receptors) also promote inflammation and fibrosis in cardiovascular tissues. Homeostasis of the RAAS is a key factor in preventing hypertension and its consequences.[79]

Phytochemical Modulation: Some dietary terpenes and polyphenols can beneficially influence RAAS activity. d-Limonene has shown antihypertensive effects in animal studies. In hypertensive rat models, lemon extract (containing limonene) supplementation led to significant reductions in systolic blood pressure and improvements in endothelial function. The proposed mechanism is limonene's metabolites acting as mild ACE inhibitors, preventing the formation of angiotensin II.[80,81] This ACE-inhibitory activity, though weaker than pharmaceutical ACE inhibitors, results in vasodilation and lower fluid retention over time. α-Pinene may directly affect vascular tone. In vitro studies of isolated artery segments report that α-pinene causes dose-dependent vasorelaxation, likely by interfering with calcium channels in smooth muscle or enhancing nitric oxide (NO) release from the endothelium.[82] Such vasodilatory action would counteract angiotensin II's vasoconstriction. Pinene also has anti-inflammatory properties that could reduce angiotensin-induced vascular inflammation.[83] 1,8-Cineole (Eucalyptol) has been observed to improve biomarkers of cardiovascular health in humans.[84] A small clinical study noted that chronic cineole intake in asthma patients not only reduced airway inflammation, but modestly lowered blood pressure and enhanced arterial oxygenation.[85] Its mechanism might involve reducing sympathetic drive (since stress and adrenergic activation feed into the RAAS) and improving endothelial responses to acetylcholine, which angiotensin II usually impairs. The combined effect of these phytochemicals is a better balanced RAAS: blood vessels remain more dilated, and the kidneys excrete more sodium, leading to normalized blood pressure. For individuals with borderline hypertension or salt-sensitive high blood pressure, integrating limonene-rich citrus oils or pinene-rich herbal extracts might aid conventional therapy. It's worth noting that these effects, while promising, are supportive, they are not as potent as prescription ACE inhibitors or angiotensin receptor blockers, but they demonstrate how diet and phytochemicals can contribute to cardiovascular homeostasis by modulating the RAAS cascade.

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[80] Wang, X., Li, G., & Shen, W. (2018). Protective effects of D-Limonene against transient cerebral ischemia in stroke-prone spontaneously hypertensive rats. *EXPERIMENTAL AND THERAPEUTIC MEDICINE*, *15*, 699-706.

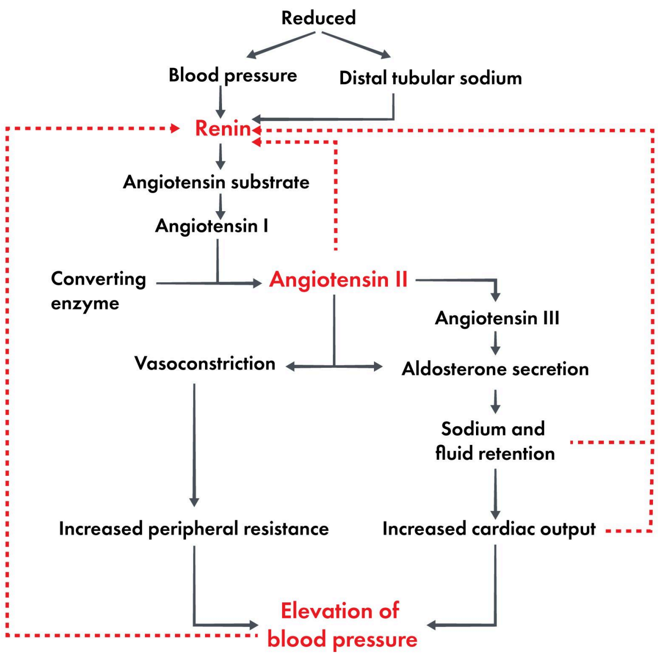
[81] Tejpal, S., Wemyss, A. M., Bastie, C. C., & Klein-Seetharaman, J. (2020). Lemon Extract Reduces Angiotensin Converting Enzyme (ACE) Expression and Activity and Increases Insulin Sensitivity and Lipolysis in Mouse Adipocytes. *Nutrients*, *12*(8), 2348.

[82] Jin, L., Xie, Z., Lorkiewicz, P., Srivastava, S., Bhatnagar, A., & Conklin, D. J. (2023). Endothelial-dependent relaxation of a-pinene and two metabolites, myrtenol and verbenol, in isolated murine blood vessels. *Am J Physiol Heart Circ Physiol*, *325*, H1446-H1460.

[83] Kim DS, Lee HJ, Jeon YD, Han YH, Kee JY, Kim HJ, Shin HJ, Kang J, Lee BS, Kim SH, Kim SJ, Park SH, Choi BM, Park SJ, Um JY, Hong SH. Alpha-Pinene Exhibits Anti-Inflammatory Activity Through the Suppression of MAPKs and the NF-κB Pathway in Mouse Peritoneal Macrophages. Am J Chin Med. 2015;43(4):731-42. doi: 10.1142/S0192415X15500457. Epub 2015 Jun 28. PMID: 26119957.

[84] Hoch, C. C., Petry, J., Griesbaum, L., Weiser, T., Werner, K., Ploch, M., ... & Wollenberg, B. (2023). 1,8-cineole (eucalyptol): A versatile phytochemical with therapeutic applications across multiple diseases. *Biomedicine & Pharmacotherapy*, *167*, 115467.

[85] Worth H, Dethlefsen U. Patients with asthma benefit from concomitant therapy with cineole: a placebo-controlled, double-blind trial. J Asthma. 2012 Oct;49(8):849-53. doi: 10.3109/02770903.2012.717657. PMID: 22978309.



Schematic representation of RASS. Renin is produced by the kidney in response to low blood pressure or sodium levels. Renin converts hepatically synthesized angiotensinogen to the relatively inactive angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE), mainly in the lungs' vascular endothelium. Angiotensin II is the key active hormone of the RAAS producing: vasoconstriction (Increases total peripheral resistance and blood pressure), stimulates aldosterone secretion from the adrenal cortex (increases sodium absorption and water retention), stimulates ADH (vasopressin) release from the posterior pituitary (promotes water retention), and enhances thirst via the hypothalamus. The end effects are increases in vascular volume, peripheral resistance, and cardiac output, resulting in an increase of blood pressure.

10. Hypothalamic–Pituitary–Adrenal (HPA) Axis

Physiological Function: The HPA axis is the body's central stress response system. It consists of the hypothalamus, pituitary gland, and adrenal cortex working in a hormonal cascade. In response to physical or emotional stress, the hypothalamus secretes corticotropin-releasing hormone (CRH), prompting the pituitary to release adrenocorticotropic hormone (ACTH). ACTH travels through the bloodstream to the adrenal glands, stimulating the release of cortisol. Cortisol is a glucocorticoid that helps mobilize energy by increasing glycogenolysis and serum glucose, suppresses non-urgent functions (like immunity and digestion), and enables the body to cope with the stressor. Acutely, this is adaptive, but if the HPA axis remains chronically activated due to ongoing stress or disruption, consistently high cortisol can lead to fatigue, anxiety, depression, and aggression; it contributes to the development of metabolic syndrome and weight gain; and can result in a disruption of immune system function, and electrolyte imbalances. A well-regulated HPA axis has a robust diurnal rhythm (high cortisol secretion in the morning, lower at night), and an efficient reduction in the system's activity with resolution of the stressor.[86,87]

Phytochemical Modulation: Phytochemicals can mitigate overactivation of the HPA axis, essentially acting as adaptogens to help normalize cortisol levels. Linalool again is prominent: inhalation of linalool-rich lavender has been shown to reduce blood cortisol concentrations increased due to stress. By engaging olfactory pathways and limbic structures, linalool likely promotes parasympathetic activity and directly dampens hypothalamic CRH release, thereby lowering downstream cortisol. This is supported by studies where stressed rats exposed to lavender aroma exhibited blunted ACTH and cortisol spikes compared to controls[88]. The endocannabinoid system is involved in HPA axis regulation, and β-Caryophyllene has emerged as a potential stress-buffering agent through its action on CB_2 receptors. Chronic stress in animals (e.g. repeated immobilization) normally elevates

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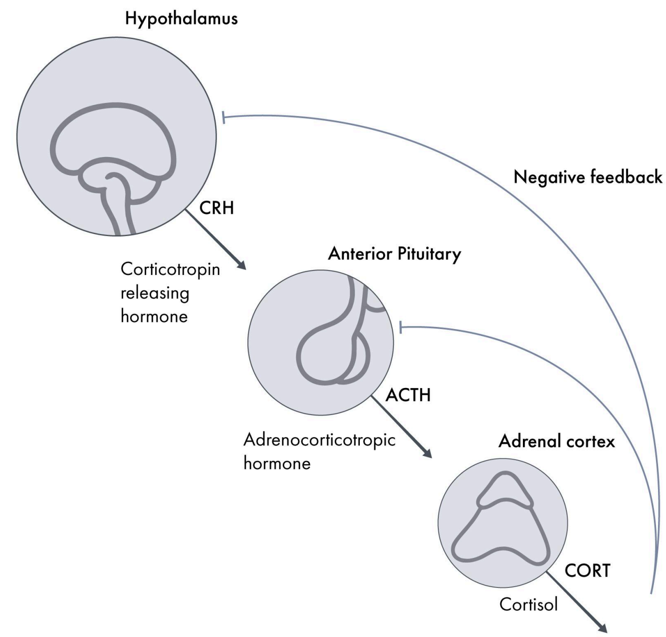
pro-inflammatory cytokines and perturbs HPA feedback,[89] but administration of β-caryophyllene in such models resulted in decreases in levels of IL-23, IL-27, and IFN-β.[90] This suggests that BCP indirectly signals the brain to decrease CRH output. Nerolidol, a tranquilizing terpene, also displays anti-stress effects. Rodent studies have found that nerolidol produces sedation and anxiolytic effects similar to diazepam,[91] which contribute to a more balanced level of HPA activity, producing more stable daily cortisol rhythms and less extreme spikes under acute stress. Clinically, these phytochemicals can be harnessed via inhalation or orally to help individuals with stress-related HPA dysregulation to manage the ensuing symptoms of burnout and chronic anxiety/depression. Patients report improved sleep, a greater sense of calm, and more balanced energy when using such remedies, outcomes consistent with healthier cortisol patterns. Over time, supporting a balanced HPA axis through these natural compounds may protect against the toll of chronic stress and improve resilience.



Schematic representation of the Hypothalamic–Pituitary–Adrenal (HPA) axis, a central stress-response system in which the hypothalamus releases corticotropin-releasing hormone (CRH), stimulating the pituitary to secrete adrenocorticotropic hormone (ACTH), which in turn prompts the adrenal cortex to produce cortisol, regulating metabolism, immune activity, and stress adaptation through feedback control mechanisms.

11. Nitric Oxide (NO) Pathway

Physiological Function: Nitric oxide is a gaseous signaling molecule that plays pivotal roles in the cardiovascular, nervous, and immune systems. Synthesized by nitric oxide synthase (NOS) enzymes (eNOS in endothelium, nNOS in neurons, iNOS in immune cells), NO diffuses freely across membranes. In blood vessels, endothelial-derived NO causes smooth muscle relaxation, leading to vasodilation and better blood flow, essential in regulating blood pressure and preventing clotting. In the brain, NO acts as a neurotransmitter/modulator involved in synaptic plasticity and memory formation. In the immune system, NO produced by macrophages helps kill pathogens but, if excessive, can contribute to inflammatory damage. Maintaining appropriate NO levels is crucial: too little (as in endothelial dysfunction) causes hypertension and

[89] Silverman, M. N., Pearce, B. D., Biron, C. A., & Miller, A. H. (2005). Immune Modulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis during Viral Infection. *Viral Immunology*, *18*(1), 41-78. doi:10.1089/vim.2005.18.41
[90] Phillips, L., Maceo Daphney, C., Oppong-Damoah, A., Uchakin, P. N., Abney, S. E., Uchakina, O. N., ... & Murnane, K. S. (2019). The cannabinoid receptor 2 agonist, β-caryophyllene, improves working memory and reduces circulating levels of specific proinflammatory cytokines in aged male mice. *Behav Brain Res*, *372*, 112012.
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atherosclerosis, whereas too much (as in sepsis or chronic inflammation) can cause oxidative damage. Balanced NO signaling supports healthy circulation, neurotransmission, and immune defense.[92]

Phytochemical Modulation: Some phytochemicals enhance beneficial NO production (e.g. in blood vessels) or reduce harmful NO-related oxidative stress. α-Pinene has demonstrated cardiovascular benefits by upregulating endothelial nitric oxide production. Studies indicate that α-pinene treatment increases expression of eNOS in vascular tissue, resulting in higher NO bioavailability and thus improved endothelium-dependent vasodilation.[93] This mechanistic insight aligns with observed blood pressure reductions in animal models given α-pinene,[94] as NO-mediated vasorelaxation alleviates hypertension and promotes perfusion of organs. Eugenol, the main terpene component of clove oil, is a potent antioxidant that directly scavenges reactive nitrogen species. In inflammatory environments. Excessive NO can react to form peroxynitrite and other radicals that damage cells. Eugenol's phenolic structure allows it to neutralize these reactive species, protecting tissues from nitrosative stress.[95] Additionally, eugenol has been noted to inhibit inducible NOS (iNOS) expression in activated immune cells, thereby reducing the flood of NO in conditions like colitis or arthritis.[96] By curbing overproduction at the source, eugenol helps prevent NO-related inflammation and pain. α-Humulene, a sesquiterpene found in hops and cannabis, exhibits anti-inflammatory properties that intersect with NO pathways. Research shows humulene suppresses key inflammatory mediators (TNF-α, IL-1β) and COX-2, which in turn can modulate iNOS activity.[97] Notably, none of these terpenes eliminate NO, that would be undesirable as NO is necessary, but rather they work to optimize NO signaling: pinene boosts endothelial NO for vascular health, while eugenol and humulene prevent NO from causing excessive inflammation. Clinically, supporting NO pathways translates to better blood pressure control,[98] enhanced cerebral blood flow (potentially improving cognition and memory),[99] and reduced inflammatory pain. For example, diets or therapies including NO-friendly phytochemicals, such as rosemary tea (contains pinene), or clove oil gargle (with eugenol) have traditionally been used for maintaining cardiovascular and oral health.[100] Modern understanding now credits, at least in part, their ability to favorably modulate nitric oxide.

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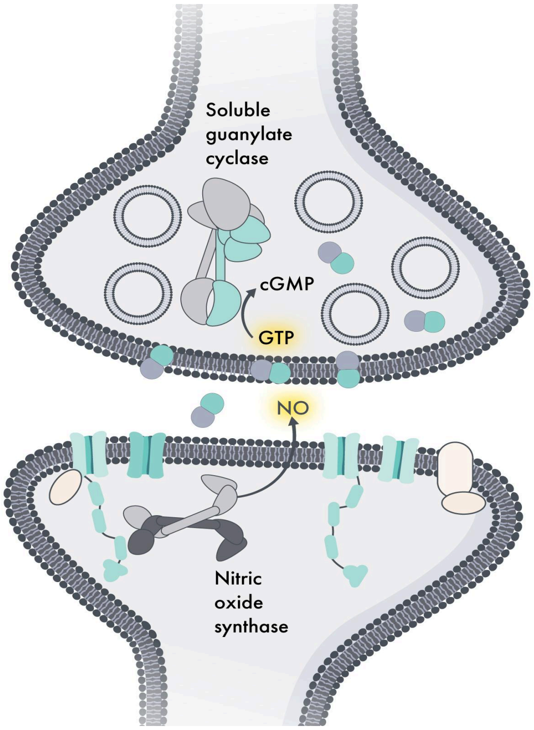

Simplified schematic representation of the human nitric oxide (NO) system, which regulates vascular tone, neurotransmission, and immune function. NO is produced by nitric oxide synthase (NOS) enzymes in endothelial, neuronal, and immune cells, acting as a signaling molecule to promote vasodilation, modulate neural activity, and influence inflammation.

12. Cytokine Signaling Pathway

Physiological Function: Cytokines are cell-signaling protein molecules, critical in coordinating the immune system and inflammation. They include pro-inflammatory cytokines (like IL-1β, IL-6, TNF-α, IFN-γ), which are released by immune cells in response to infection or injury to amplify immune responses[101] (fever, tissue recruitment of white blood cells, etc.), and anti-inflammatory cytokines (like IL-10, TGF-β) that help resolve inflammation and promote healing.[102] In normal homeostasis, cytokines orchestrate the launch of defense mechanisms and the subsequent return to baseline once a threat is cleared. However, chronic elevation of pro-inflammatory cytokines is implicated in a host of diseases: autoimmune conditions, metabolic syndrome,[103] depression (the "cytokine hypothesis"),[104] and neurodegeneration,[105] as they create sustained tissue damage and dysregulation. Thus, maintaining a balanced cytokine system, which produces an efficient acute response and timely resolution, is vital for health.

Phytochemical Modulation: Many phytochemicals exhibit immunomodulatory effects, tamping down excessive cytokine production or shifting the balance toward resolution. β-Caryophyllene, a CB_2 agonist, is notable for its broad anti-inflammatory action, and administration of BCP leads to lowered release of pro-inflammatory cytokines. In rodent models of inflammation, β-caryophyllene treatment significantly reduced levels of IL-1β, IL-6, and TNF-α in affected tissues.[106] By engaging CB_2, BCP inhibits NF-κB and other signaling pathways that drive cytokine gene expression, yielding a more anti-inflammatory state. This has been demonstrated in models of arthritis and colitis, where BCP curbed cytokine-mediated tissue injury and improved symptoms.[107] Humulene also

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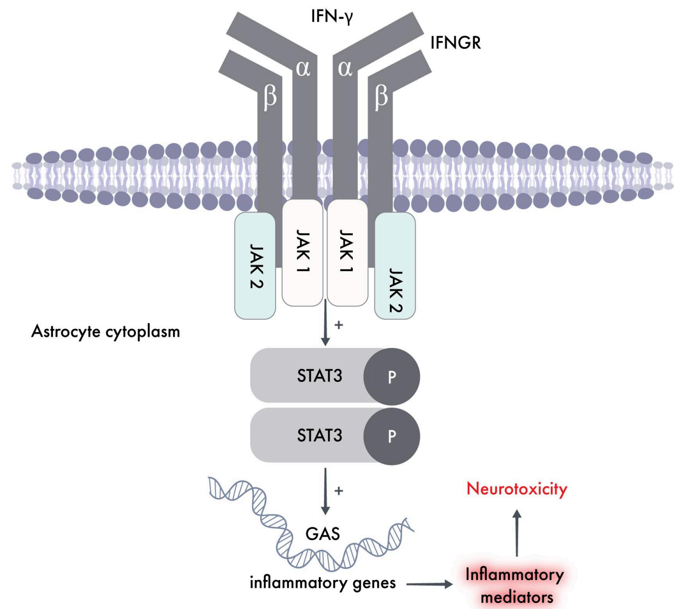
shows a capacity to selectively suppress cytokine production. In one study, humulene effectively reduced TNF-α, prostaglandin E_2 and IL-1β release from activated macrophages.[108] The dual blockade of cytokine and eicosanoid pathways by humulene translated to reduced edema and inflammatory pain in animals.[109] Eugenol, besides its antioxidant role, directly targets the master regulator NF-κB, a transcription factor that, when activated by stressors, induces activation of pro-inflammatory cytokine genes. Eugenol, in cell studies, prevented activation of NF-κB in response to the LPS bacterial toxin. Consequently, cells treated with eugenol produced far less TNF-α, IL-6, and nitric oxide compared to untreated cells during an inflammatory challenge.[110] This NF-κB inhibition underlies clove oil's traditional use to soothe inflammatory ailments like toothaches or sore throats.[111] Summarizing, these plant compounds do not indiscriminately suppress the immune system; rather, they fine-tune cytokine signaling by damping excessive or unnecessary pro-inflammatory signals while sometimes boosting anti-inflammatory ones. For individuals with chronic low-grade inflammation (e.g. metabolic syndrome, arthritis, stress-related inflammation), integrating such phytochemicals can help lower systemic cytokine levels and improve outcomes. Indeed, trials of essential oils and dietary spices rich in these compounds have revealed reductions in inflammatory biomarkers.[112] BlissThera provides a milieu of these synergistic phytochemicals, aiming to restore immunological homeostasis, where excessive cytokine production is moderated and healing processes are supported.



Schematic representation of inflammatory cytokine IFN-γ–mediated JAK–STAT3 signaling in human astrocytes. IFN-γ binds to the IFNGR receptor complex, activating JAK family kinases, which phosphorylate STAT3. Phosphorylated STAT3 dimerizes and translocates to the nucleus, where it binds to γ-activated sequence (GAS) elements and drives expression of inflammatory mediators that contribute to astrocyte-induced neurotoxicity.

Homeostasis in Practice: Applying the Framework

Taken together, these twelve systems represent the major regulatory hubs through which the body maintains homeostasis. While each system has been examined individually, they do not operate in isolation. The true therapeutic potential of BlissThera lies in its capacity to engage these systems simultaneously—using synergistic phytochemical inputs that reflect the complexity of

Neuroinflammation and Neurodegeneration. *Int. J. Mol. Sci.* 2025, *26*, 6027.

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natural environments. Rather than targeting a single symptom or receptor, BlissThera leverages the body's own interconnected regulatory architecture, supporting balance across multiple pathways in tandem. This systems-level engagement provides the foundation for its clinical efficacy and helps explain the progressive, cumulative therapeutic responses observed in practice. The following sections shift focus from molecular mechanisms to clinical outcomes—exploring how BlissThera BINA therapy is implemented, how patients respond over time, and how this nature-informed modality can complement existing care strategies.

Clinical Framework and Cumulative Response Patterns

Using BlissThera's proprietary micro-processor controlled hardware, device software and EMR, BINA therapy sessions are typically initiated on a weekly basis, with frequency and formulation adjusted in response to individual symptom profiles and treatment progression. Patients commonly report progressive improvements in symptom intensity, frequency, and duration over time. Notably, these benefits tend to accumulate: an initial session may offer relief lasting several hours to days, while subsequent sessions extend the duration of benefit and reduce baseline symptom recurrence between treatments. This cumulative response pattern is a defining feature of BlissThera's clinical value, indicating long-term recalibration and restoration of homeostatic systems rather than a transient pharmacologic effect.[113]

Equally important, the safety and tolerability profile of BlissThera has been excellent in clinical settings. No significant adverse events have been reported with the use of its natural botanical formulations. A few patients experience mild, transient sedation or euphoria during or shortly after sessions which quickly resolve. Overall, patients consistently describe the therapy as both pleasant and calming, enhancing compliance and supporting its role as a sustainable adjunctive modality.[114]

The condition-specific vapor-phase phytochemical profiles delivered through BlissThera's BINA therapy are engineered to harness synergistic interactions among plant-derived compounds. These synergistic effects engage multiple regulatory systems simultaneously—neuroendocrine, immune, vascular, and autonomic—to produce targeted yet holistic therapeutic outcomes. When administered consistently over time, BlissThera's BINA therapy has shown to support a cumulative recalibration of homeostatic function[115], reinforcing the body's capacity to maintain internal balance across a range of physiologic domains.[116]

Virtual Nature and Virtual Forest Bathing

To amplify therapeutic outcomes, the BlissThera system integrates optional immersive digital environments with BINA therapy, creating a multi-sensory "virtual forest bathing" experience. Patients receive treatment within a calming, nature-based audiovisual simulation that includes panoramic forest visuals, ambient nature sounds, and subtle climate cues—while simultaneously inhaling symptom-targeted phytochemical formulations delivered via the BlissThera vapor-phase system. This integration mirrors and enhances the core principles of Forest Medicine's Shinrin-Yoku (forest bathing), offering a clinically replicable version of the forest's healing milieu.

In addition to the above mentioned clinical documentation on the benefits of forest exposure, the therapeutic value of visual and auditory exposure to nature is also well supported. Studies show that urban green and blue spaces—such as parks, gardens, and waterfronts—confer measurable health benefits[117]. Even passive

113 BlissThera Clinical Case Reports

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115 BlissThera Clinical Case Reports
116 BlissThera Clinical Case Reports
117 Kabisch, N., van den Bosch, M., & Lafortezza, R. (2017). The health benefits of nature-based solutions to urbanization

exposure, such as viewing greenery through a window, has been associated with faster post-operative recovery, reduced analgesic use, and more positive mood indicators.[118,119] Virtual reality (VR) platforms simulating natural environments have been used successfully to reduce stress and anxiety across diverse patient populations, including individuals with cancer, dementia, and substance use disorders. Notably, VR-based nature content has been found to outperform urban-themed VR environments in promoting relaxation and emotional well-being.[120]

BlissThera implements this integrative approach by pairing curated virtual environments with vapor-phase botanical delivery, supported by optional geophilic EMF frequency exposure. Patients often describe the sessions as deeply immersive and restorative, akin to stepping into a tranquil woodland. This layered sensory input enhances parasympathetic activation, engages limbic system pathways, and reinforces the therapeutic impact of phytochemical modulation.[121]

This therapeutic model enables consistent forest-based interventions accessible in any setting—urban clinic or home—regardless of climate or geography. Additionally, by delivering BINA's concentrated, condition-specific phytochemical doses alongside immersive natural simulations, BlissThera compresses the physiological and psychological advantages of extended wilderness exposure into brief, clinically practical sessions. This nature-technology synergy allows consistent, scalable access to the therapeutic essence of the forest, serving as a bridge between ancestral healing traditions and the precision tools of modern integrative medicine.

Integration with Modern Medicine

BlissThera's approach aligns closely with the goals of personalized, integrative medicine, making it a valuable adjunct in the treatment of a wide range of conditions. Rather than only targeting a single symptom or organ system, BlissThera's multi-pathway modulation supports the *whole-body* homeostasis; dysregulation of proper homeostasis underlies many chronic diseases.[122]

Its use of condition-specific algorithms means that therapy can be individualized for each patient's conditions and symptoms. For instance, one formulation may prioritize anxiolytic and antidepressant phytochemistry for a patient with PTSD and insomnia, while another emphasizes bronchodilation and anti-inflammatory compounds for a patient with COPD and arthritis.[123] In this way, clinicians can incorporate BlissThera into treatment plans for chronic pain, anxiety disorders, depression, hypertension, pulmonary disease, inflammatory and autoimmune conditions, neurodegenerative diseases, and more using specific therapy algorithms that best complement the patient's conventional therapies.[124]

By working to normalize the body's endogenous regulatory systems, BlissThera can *enhance overall resilience and symptom control* without the risk of destabilizing any single pathway. As such, it is especially useful as a complementary therapy—supporting pharmacologic treatment, while also offering potential for dose reduction where clinically appropriate.

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[120] Syed Abdullah, S. S., Awang Rambli, D. R., Sulaiman, S., Alyan, E., Merienne, F., & Mohd Muhaiyuddin, N. D. (2021). The Impact of Virtual Nature Therapy on Stress Responses: A Systematic Qualitative Review. *Forests*, *12*(12), 1776.

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[123] BlissThera Clinical Case Reports

[124] BlissThera Clinical Case Reports

Clinical observations have documented cases in which patients, under medical supervision, have successfully reduced or discontinued medications including opioids, benzodiazepines, SSRIs, NSAIDs, and anticonvulsants following sustained use of BlissThera.[125] By combining targeted pharmaceutical interventions with broad-spectrum phytochemical regulation, this integrative approach has the potential to achieve clinical outcomes that neither modality alone may fully deliver.

BlissThera's strong safety profile further supports its ease of integration into existing care frameworks. All phytochemical components are derived from botanical sources with established human safety profiles; classified as Generally Recognized As Safe (GRAS) by the U.S. FDA. Much like a natural forest atmosphere, these vapor-phase formulations are delivered in micro-doses, carefully calibrated to remain well below known irritant thresholds. As a result, patients of varying ages and states of health tolerate BlissThera well, and there have been no reports of serious adverse events in clinical use.

BlissThera has been co-administered with a range of pharmacotherapies—including opioids, SSRIs, anti-inflammatories, anticonvulsants, and cannabinoid formulations—without evidence of adverse interactions.[126] This compatibility allows for seamless incorporation into a patient's ongoing care plan. For many, the combined approach of conventional medical treatment and BlissThera therapy yields enhanced symptom relief, improved mood, sleep quality, and daily function—particularly in cases where standard interventions have plateaued.[127] With its high tolerability, low interaction risk, and scalable implementation, BlissThera offers practitioners a flexible therapeutic tool that can be individualized and adjusted to support evolving patient needs.

Conclusion

In summary, this paper has explored the physiological roles and phytochemical modulation of twelve key homeostatic pathways—spanning major neurotransmitter systems, endocrine networks, vascular regulators, and immune mediators. For each of these interconnected systems, specific phytochemicals were identified that influence critical signaling cascades, illustrating how BlissThera's multi-component formulations engage distinct receptors and feedback mechanisms *to help restore physiological balance and optimal function*.

Rather than acting as a single-targeted pharmaceutical, BlissThera's vapor-phase phytochemical formulations exert a broad yet nuanced influence on the body's internal chemistry—attenuating overactive processes while amplifying underactive ones, ultimately guiding the organism back toward a more stable homeostatic equilibrium. By applying a palette of evidence-supported phytochemicals, BlissThera BINA therapy offers a holistic, systems-level approach to normalize stress responses, reduce inflammation, stabilize neurochemical function, and improve pain regulation.

The therapeutic model is rooted in *synergy*: while individual phytochemicals may produce modest effects alone, when precisely combined, their actions reinforce and potentiate one another, yielding a cumulative impact greater than the sum of their parts.[128] Delivered in concert with immersive natural environment cues, this plant-based strategy represents a contemporary implementation of traditional botanical medicine, reimagined through the lens of modern clinical practice and physiological science, aimed at re-establishing *multisystem homeostasis*. In essence, BlissThera harnesses the therapeutic power of phytochemical atmospheres to support the body's innate capacity for regulation, repair, and resilience. The result is a gentle yet profound modality that can serve as a valuable adjunct, or

[125] BlissThera Clinical Case Reports
[126] BlissThera Clinical Case Reports
[127] BlissThera Clinical Case Reports

[128] Borges e Soares, G. A., Bhattacharya, T., Chakrabarti, T., Tagde, P., & Cavalu, S. (2022). Exploring Pharmacological Mechanisms of Essential Oils on the Central Nervous System. *Plants*, *11*(1), 21.

in some cases as an alternative, to conventional pharmacotherapy, especially for complex chronic conditions where multiple physiological systems are typically affected.[129]

Already in use in select integrative medicine clinics, BlissThera functions as part of a personalized care model, with therapy regimens tailored to each patient's physiological profile, symptoms, and goals. Its ability to modulate multiple homeostatic systems simultaneously enables it to address a diverse range of conditions—from chronic pain and anxiety to systemic inflammation and cognitive dysfunction. By targeting the body's regulatory networks rather than isolated symptoms, BlissThera offers a complementary or alternative pathway for patients whose needs are unmet by conventional pharmacologic care alone.

As this nature-informed, technology-assisted modality continues to gain clinical traction, it holds the potential to reshape how chronic and stress-related conditions are managed—serving as a scalable therapeutic bridge between ancestral botanical wisdom and the personalized medicine models of the future.

[129] BlissThera Clinical Case Reports