The Service Dog as Living Adaptogen: Comparative HPA Axis Modulation Through Botanical and Bond-Based Naturopathic Interventions

John Bellocchio, M.Phil., Ed.S., C.A., CCDT, PPG, NALA, NALS

bellocchioj@outlook.com

May 2026

Abstract

The hypothalamic-pituitary-adrenal (HPA) axis sits at the center of contemporary naturopathic stress medicine, and the botanical adaptogens — chiefly *Withania somnifera* (ashwagandha) and *Rhodiola rosea* — have become the field's first-line agents for its modulation. Yet two developments threaten the coherence of this single-track therapeutic paradigm. First, Albalawi's 2025 meta-analysis of seven randomized controlled trials demonstrated a clinically meaningful reduction in serum cortisol (−1.16 µg/dL, 95% CI: −1.64 to −0.69, $p<0.001$) but no statistically significant change in perceived stress (SMD = −0.355, 95% CI: −1.188 to 0.47, $p=0.40$), exposing what this paper will call the cortisol-perception disconnect. Second, ashwagandha's safety profile has deteriorated sharply, with a 2023 Danish ban, a June 2024 EU Heads of Food Safety Agencies (HoA) recommendation prioritizing the herb for Article 8 review, and a growing case series of herb-induced liver injury including three fatal acute-on-chronic liver failure cases in a single Indian cohort. A largely independent literature on the human-animal bond — anchored by the Purdue University / University of Arizona Center for the Human-Animal Bond research program and the Nagasawa oxytocin-gaze findings — has produced rigorous physiological evidence that service dog partnerships normalize the cortisol awakening response (CAR), activate the central oxytocinergic system, and modulate the same HPA pathways that adaptogens target. This paper offers the first comparative analytic synthesis of those two literatures within naturopathic clinical theory. It argues that the service dog partnership functions as a *living adaptogen* — an endogenous, bond-based modifier of stress reactivity that operates through *vis medicatrix naturae*, the body's innate healing capacity activated through an evolved interspecies relationship. Three original contributions are advanced: (1) the first published framing of the human-animal bond as a naturopathic stress intervention operating through *vis*

medicatrix naturae; (2) a comparative mechanistic analysis revealing that the field's reliance on cortisol as the sole marker of adaptogenic efficacy is no longer defensible; and (3) the identification of vision-impaired guide dog handlers as an unstudied population establishing a concrete future research agenda.

Keywords: adaptogens; *Withania somnifera*; *Rhodiola rosea*; cortisol awakening response; HPA axis; human-animal bond; service dog; guide dog; oxytocin; *vis medicatrix naturae*; naturopathic medicine; psychoneuroendocrinology; network pharmacology.

1. Introduction

For more than a century the naturopathic profession has grounded its clinical reasoning about chronic stress in a vitalist premise — that the organism possesses an inherent ordering capacity, *vis medicatrix naturae*, which the physician's role is to support rather than supplant [1,2]. In the twentieth century that premise was operationalized into the modern category of "adaptogens." The term was coined by Lazarev in 1947 and given its plant-pharmacological criteria by Brekhman and Dardymov, who in *Annual Review of Pharmacology* in 1969 described "new substances of plant origin which increase nonspecific resistance" — innocuous medicinal plants that normalize body functions in response to harmful environmental conditions without producing a specific pharmacological effect on any single target organ [3]. The category has proven extraordinarily durable. As Panossian and colleagues have shown across two decades of work, adaptogens such as *Withania somnifera*, *Rhodiola rosea*, *Eleutherococcus senticosus*, and *Schisandra chinensis* operate as polyvalent network-pharmacological agents that act simultaneously on heat-shock proteins (Hsp70 and Hsp25), neuropeptide Y, NF-κB, FOXO3/DAF-16, nitric oxide signaling, stress-activated protein kinases, and the corticosteroid receptor system [4,5,6]. They are, in Panossian's careful 2017 formulation in *Annals of the New York Academy of Sciences*, "stress-response modifiers that increase an organism's nonspecific resistance to stress by increasing its ability to adapt and survive" — and the reductionist single-receptor model of pharmacology is structurally incapable of describing how they work. Panossian writes plainly that "the mechanisms of action of adaptogens are impossible to rationally describe using the reductionist concept of pharmacology, whereas the network pharmacology approach is the most suitable method" [5].

This is the literature that defines the current state of adaptogenic medicine. It is also a literature now under significant pressure on two fronts.

The first pressure is empirical. Albalawi's 2025 PRISMA-compliant meta-analysis of seven randomized controlled trials, published in *Nutrition and Health*, reported a robust pooled reduction in serum cortisol of −1.16 µg/dL (95% CI: −1.64 to −0.69, $p<0.001$) following ashwagandha supplementation, but found no statistically significant effect on the Perceived Stress Scale across the same trials (SMD = −0.355, 95% CI: −1.188 to 0.47, $p=0.40$) [7]. This is what I will refer to throughout the paper as the cortisol-perception disconnect. Other recent meta-analyses, including Arumugam and colleagues' 2024 *Explore* synthesis (n=558 across nine trials, doses 125–600 mg/day for 30–90 days, with reported mean differences of −4.72 for PSS, −2.19 for the Hamilton Anxiety Scale, and −2.58 for serum cortisol), have produced more favorable subjective endpoints [8]; but the heterogeneity is itself the point. The field's single most-used biomarker for adaptogenic efficacy — total serum cortisol — does not reliably translate into the lived experience of being less stressed.

The second pressure is regulatory and toxicological. A 2020 risk assessment by the Technical University of Denmark (DTU) National Food Institute concluded that no safe lower limit of ashwagandha intake could be established, citing evidence for effects on thyroid hormones, sex hormones, and reproductive function; in April 2023 the Danish Veterinary and Food Administration (Fødevarestyrelsen) banned the herb in dietary supplements, the first such ban in the European Union [9,10]. In June 2024 the EU Heads of Food Safety Agencies (HoA) Working Group on Food Supplements formally recommended prioritizing ashwagandha for an Article 8 procedure under Regulation (EC) No 1925/2006 "due to (potential) effects on reproduction, thyroid hormones, acetylcholinesterase, the immune system and due to liver

toxicity. The toxicity data are limited and insufficient to derive a safe dose level or health-based guidance value" [11]. Philips and colleagues' 2023 *Hepatology Communications* case series, the largest from a single national context, retrospectively analyzed twenty-three patients with ashwagandha-related liver injury at multiple Indian centers between January 2019 and December 2022 and reported in detail on eight cases of single-ingredient formulation hepatotoxicity, of whom three presented with acute-on-chronic liver failure and "all 3 died on follow-up" [12]. The cumulative VigiBase signal, supplemented by ANSES (France), RIVM (Netherlands), the Swedish Food Agency, and Australian Therapeutic Goods Administration advisories, now exceeds seventy reports of hepatobiliary disorders associated with the herb [11,13].

A profession committed to *primum non nocere* cannot ignore this combination of pressures. If the field's flagship botanical adaptogen reduces a biomarker without reliably reducing the patient's experience of stress, and if it does so at a hepatotoxic and endocrine cost that has triggered a cascade of European bans and warnings, then the question of what else lies within the adaptogenic category — and within the broader naturopathic repertoire of stress interventions — is no longer academic.

A largely parallel research literature, conducted by investigators who do not generally identify with naturopathic medicine, has been producing exactly such an alternative. Rodriguez, Nieforth, O'Haire, and colleagues at the Purdue University / University of Arizona Center for the Human-Animal Bond have over the past decade conducted the first rigorous longitudinal physiological studies of psychiatric service dogs in veterans with posttraumatic stress disorder [14,15]. Their 2024 *Scientific Reports* trial (NCT03245814) — the largest of its kind, assessing 245 participants at baseline and three-month follow-up across an intervention group (88 service-dog-paired veterans and 46 partners) and a usual-care control group (73 veterans and 38

partners) — demonstrated that veterans paired with a service dog showed a significantly higher cortisol awakening response than veterans receiving usual care alone, in both the area under the curve with respect to increase (AUCi β=1.46, SE=0.73, p=0.046) and the absolute increase from waking (AINC β=0.05, SE=0.02, p=0.035) [14]. In a population whose stress pathology is characterized precisely by a blunted CAR, this represents a measurable physiological normalization of HPA axis function attributable to the human-animal partnership. Independently, Nagasawa and colleagues' 2015 *Science* paper documented a species-specific oxytocin-gaze positive feedback loop between humans and dogs that does not exist between humans and wolves, finding that "gazing behavior from dogs, but not wolves, increased urinary oxytocin concentrations in owners, which consequently facilitated owners' affiliation and increased oxytocin concentration in dogs" [16]. Beetz and colleagues' 2012 *Frontiers in Psychology* review of sixty-nine original peer-reviewed studies established that oxytocin system activation is the leading mechanistic candidate for the documented psychophysiological effects of human-animal interaction; the authors propose explicitly that "the activation of the oxytocin system plays a key role in the majority of these reported psychological and psychophysiological effects of HAI" [17]. Gnanadesikan and colleagues' 2024 *Psychoneuroendocrinology* paper extended the oxytocin findings to children and unfamiliar dogs using both salivary and urinary assays [18].

Two literatures, two professional communities, one HPA axis. No published work has connected them to naturopathic medicine's vitalist tradition.

This paper makes that connection. It argues that the service dog partnership is best understood within naturopathic theory as a *living adaptogen* — a non-pharmacological but mechanistically convergent intervention that modifies HPA axis reactivity through endogenous oxytocinergic and behavioral pathways, and that does so as the most direct contemporary

expression of *vis medicatrix naturae*: the body's innate healing capacity activated through an evolved interspecies relationship. The argument is organized in three parts. Part I reviews the current state of adaptogenic medicine, with particular attention to the cortisol-perception disconnect, Panossian's network pharmacology framework, the emerging gut microbiome literature, and the unfolding ashwagandha safety crisis. Part II reviews the human-animal bond literature as it bears on HPA axis modulation, with particular attention to the Purdue/Arizona cortisol awakening response work, the oxytocin-gaze loop, the broader psychoneuroimmunological evidence base, and what I will identify as a critical and field-defining gap: the complete absence of physiological stress biomarker studies in vision-impaired guide dog handlers. Part III synthesizes the two literatures within naturopathic clinical theory and proposes an integrated clinical model.

The three original contributions of the paper, made explicit at the outset, are: (1) the first published framing of the human-animal bond as a naturopathic stress intervention operating through *vis medicatrix naturae*; (2) a comparative mechanistic analysis showing that the field's reliance on cortisol as the sole marker of adaptogenic efficacy is no longer defensible; and (3) the identification of vision-impaired guide dog handlers as an unstudied population whose physiological stress biomarkers offer the cleanest available natural experiment for testing the claim that the human-animal bond functions adaptogenically.

2. Materials and Methods

This is a literature-based comparative analytic review. The methodological design departs from a standard scoping or systematic review in three respects. First, it deliberately spans three research domains that are rarely cited together: adaptogenic pharmacology, the psychoneuroendocrinology of the human-animal bond, and naturopathic clinical theory. Second,

its primary output is conceptual rather than statistical: it produces a comparative mechanistic framework and an integrated clinical model, not a pooled effect estimate. Third, it explicitly attempts to bridge a vitalist clinical tradition with contemporary biomedical evidence, and therefore treats the foundational naturopathic literature on *vis medicatrix naturae* as primary source material on par with peer-reviewed mechanistic studies.

2.1 Search strategy

Searches were conducted between October 2025 and April 2026 across PubMed, Google Scholar, ScienceDirect, the Cochrane Library, and the open archives of the integrative and naturopathic medicine journals (including *Integrative Medicine: A Clinician's Journal*, *Phytomedicine*, *Pharmaceuticals*, *Frontiers in Psychology*, *Frontiers in Veterinary Science*, *Psychoneuroendocrinology*, *Hepatology Communications*, *Annals of the New York Academy of Sciences*, and the *American Journal of Medicine*). An AI-assisted search workflow was used to disambiguate overlapping author networks — particularly the Panossian/Wikman/Efferth pharmacology corpus and the Rodriguez/Nieforth/O'Haire human-animal bond corpus — and to surface 2025–2026 publications that had not yet been fully indexed in legacy databases at the time of initial searching.

Search terms were combined in three families. The *adaptogenic family* included "adaptogen," "*Withania somnifera*," "ashwagandha," "*Rhodiola rosea*," "network pharmacology," "HPA axis," "cortisol," "perceived stress," "Hsp70," "neuropeptide Y," "FOXO3," "hepatotoxicity," "Danish ban," "EFSA," and "QSAR." The *human-animal bond family* included "service dog," "guide dog," "psychiatric assistance dog," "animal-assisted intervention," "cortisol awakening response," "oxytocin," "human-animal interaction," "Nagasawa," "Purdue Center for the Human-Animal Bond," and "PTSD service dog." The *naturopathic theory family* included

"*vis medicatrix naturae*," "naturopathic principles," "vitalism," "Hippocratic," "Lindlahr," "Pizzorno," and "healing power of nature."

Priority was given to peer-reviewed publications from 2020 through 2026, with foundational references — for example Brekhman and Dardymov 1969 [3]; Panossian and Wikman 2010 [6]; Beetz et al. 2012 [17]; Nagasawa et al. 2015 [16] — retained where they anchored a mechanistic claim that more recent work has not superseded. Regulatory documents (DTU, EU HoA, ANSES, RIVM) were consulted as primary sources for the safety section.

2.2 The five-dimension comparative framework

Botanical adaptogens and the human-animal bond are compared along five dimensions: (1) mechanism of HPA axis modulation — the specific receptor systems, signaling pathways, and central nervous system circuits engaged; (2) biomarker evidence — what cortisol, oxytocin, and downstream measures show, and where the literatures converge and diverge; (3) onset and duration of effect — acute versus chronic, and dose-response or "dose-equivalent" considerations; (4) safety profile — adverse events, regulatory status, and contraindications; and (5) alignment with naturopathic principles — first do no harm, healing power of nature, treat the cause, doctor as teacher, treat the whole person, prevention, and wellness. The framework is applied descriptively in Parts I and II and synthetically in Part III.

2.3 Author positionality

I write as a credentialed practitioner-researcher whose work spans cognition, integrative health, and applied animal behavior. As a Certified Canine Dog Trainer (CCDT) with specialized work in vision-impaired canine populations, I bring direct clinical observation to bear on the human-animal bond literature, particularly in Parts II and III, where the absence of physiological

biomarker work in guide dog handlers is — to my knowledge — first identified in print in this paper. This positionality is methodologically relevant: the integrated clinical model proposed in Part III is informed by, but not derived from, individual case observations, and the paper does not report patient data.

PART I: THE STATE OF ADAPTOGENIC MEDICINE

3. Botanical Adaptogens as HPA Axis Modulators

3.1 The category and its mechanistic reframing

The category "adaptogen" is now nearly six decades old in its modern plant-pharmacological sense. Its original Brekhman-Dardymov formulation — innocuous medicinal plants that normalize body functions in response to harmful environmental conditions — captured an empirical observation, not a mechanism [3,6]. For four decades, attempts to give the category a mechanism remained essentially reductionist: investigators asked which receptor a single adaptogenic constituent (a withanolide, a salidroside, a rosavin, a ginsenoside) bound to, and which downstream cascade was thereby activated. That approach generated a great deal of useful biochemistry but never explained the central clinical observation about adaptogens, namely that they appear to do different and even opposite things in different physiological contexts — calming an over-aroused patient and energizing a fatigued one, on the same dose.

Panossian's principal contribution, advanced most directly in his 2017 *Annals of the New York Academy of Sciences* paper and elaborated through the 2025 *Pharmaceuticals* analyses [4,5], has been to argue that this contextual reversibility is not an artifact of inadequate dosing studies but a structural property of how the molecules act. The 2017 paper identifies the following mediators as "key players in mediating the adaptogenic effects of plant extracts": "the

stress hormones cortisol and neuropeptide Y (NPY) and several important mediators of the adaptive stress response (e.g., nitric oxide, stress-activated protein kinases, heat shock proteins (HSP70 and HSP25), and the FOXO (DAF-16) transcription factor)" [5]. Subsequent network analyses have added NF-κB and G protein-coupled receptor cascades to the list, and have specified the two major chemical groups of adaptogens — phenolic phenethyl and phenylpropanoid derivatives (chemically related to monoamine neurotransmitters of the sympathoadrenal system: epinephrine, norepinephrine, dopamine) and tetracyclic and pentacyclic glycosides (chemically related to steroid hormones: cortisol, testosterone, estradiol) [4]. The therapeutic action of any given adaptogen is the integrated outcome of small-magnitude effects on a large number of these mediators simultaneously — what Panossian and colleagues describe as the "polyvalent action and the pleiotropic pharmacological activity of adaptogens" [4].

This reframing is consequential. It explains why no single biomarker — including the field's most-cited one, total serum cortisol — should be expected to capture an adaptogen's full effect. It also explains why blinded randomized controlled trials of single endpoints often produce equivocal results: they are testing a single-target model against compounds that do not have a single target. The disconnect between the network-pharmacological reality of the molecules and the single-endpoint design of the trials that test them is the structural source of the heterogeneity that has plagued the field.

3.2 Recent clinical trial evidence for ashwagandha

Despite the mechanistic complexity, ashwagandha has accumulated a substantial RCT base for stress and anxiety endpoints. Arumugam and colleagues' 2024 *Explore* meta-analysis pooled nine studies (n=558) and reported significant reductions in Perceived Stress Scale (mean difference

−4.72), Hamilton Anxiety Scale (−2.19), and serum cortisol (−2.58), at doses of 125–600 mg/day for 30–90 days, across both root-only and root-plus-leaf formulations, concluding that ashwagandha was "generally safe with some mild side effects" [8]. Bachour and colleagues' 2025 BJPsych Open systematic review of fifteen RCTs (n=873) drew similar conclusions on cortisol, stress, and anxiety endpoints [19]. Pandit and colleagues' 2024 *Nutrients* randomized controlled trial in chronically stressed adults extended this work and provided additional dosing detail [20].

Against this generally favorable picture, Albalawi's 2025 meta-analysis is the methodologically tightest recent contribution [7]. It applied PRISMA guidelines to seven cortisol-reporting and six PSS-reporting trials (n=488), used the Cochrane Risk of Bias 2 tool, and reported the cortisol-perception disconnect already noted: −1.16 μg/dL on cortisol ($p<0.001$) but null on the PSS ($p=0.40$), with moderate heterogeneity ($I^2=50.9\%$). The methodological reason that Albalawi's analysis is taken seriously here is its restrictive inclusion criteria (RCTs of ≥2 weeks duration, oral doses ≥250 mg/day, both cortisol and PSS outcomes reported) and its explicit interrogation of the cortisol-versus-perception question, which most prior meta-analyses had pooled or papered over.

Several explanations for the disconnect are plausible. The treatment durations may simply be too short for subjective stress to track an underlying cortisol normalization. Inclusion criteria varied in their definition of stress at baseline. The PSS itself may be insensitive to the kind of physiological change ashwagandha produces. But the most theoretically interesting possibility — and the one this paper develops — is that we have been asking ashwagandha to do something a stress-buffering molecule does not do on its own: produce the felt sense of being held, supported, and safe that meaningfully reduces perceived stress in humans. That felt sense, as Part II will show, is canonically produced by oxytocinergic social interaction, and is precisely

what the human-animal bond literature has been measuring on the other side of the disciplinary wall.

3.3 Rhodiola rosea and the broader adaptogenic family

Rhodiola rosea has a smaller but methodologically more longstanding RCT base than ashwagandha. Ishaque and colleagues' 2012 *BMC Complementary and Alternative Medicine* systematic review identified eleven controlled trials, of which two of six in healthy physical-fatigue populations and three of five in mental-fatigue populations reported significant *Rhodiola* effects, with the caveat that all included studies showed either high or unclear risk of bias [21]. The European Medicines Agency Committee on Herbal Medicinal Products approved a *Rhodiola rosea* root and rhizome traditional-use registration in 2011 for the temporary relief of stress symptoms such as fatigue and weakness, on the basis of long-standing traditional use and a generally favorable safety profile [21].

Mechanistically, *Rhodiola*'s principal active constituents — rosavins and salidroside — fall within Panossian's "phenolic phenethyl and phenylpropanoid derivatives" group, which the 2025 network analysis associates with monoamine neurotransmitter signaling [4]. *Rhodiola* is therefore mechanistically complementary to, rather than redundant with, ashwagandha, whose withanolide constituents fall into the tetracyclic and pentacyclic glycoside group and act preferentially on steroid-hormone-related signaling [4]. The Panossian and Wikman 2010 review remains the canonical statement of the broader CNS effects: adaptogens "exhibit neuroprotective, anti-fatigue, antidepressive, anxiolytic, nootropic and CNS stimulating activity" through mechanisms that include Hsp70 induction and modulation of stress-activated protein kinase signaling [6].

The 2025 Panossian, Lemerond, and Efferth *Pharmaceuticals* paper on adaptogens in long-lasting brain fatigue extends the framework explicitly to post-stroke, post-traumatic brain injury, and aging-related chronic low-grade inflammatory disorders, arguing that adaptogens "trigger the defense adaptive stress response that leads to the extension of the limits of resilience to overload" [22]. This is, in effect, a maturing statement of how the network pharmacology framework links the molecular-level action of adaptogens to the clinical phenomenology of chronic stress syndromes that most patients and most naturopaths actually encounter.

3.4 The emerging gut microbiome literature

A third development reframes the entire mechanistic discussion. A growing body of work in 2024–2025 suggests that a substantial fraction of adaptogen efficacy may be mediated not directly through CNS receptors but through gut microbiome modulation. Bharani and colleagues' 2025 randomized double-blind placebo-controlled trial in geriatric Beagles, published in *Frontiers in Veterinary Science*, demonstrated that ashwagandha root extract (high-withanolide KSM-66 preparation) administration over sixty days produced statistically significant shifts in fecal microbial metabolites consistent with improved gut barrier function and reduced systemic inflammation [23]. The companion 2025 *Applied Sciences* systematic review on psychobiotics and adaptogens articulates the gut-brain framing in detail, noting that adaptogenic effects on mood, fatigue, and stress reactivity may be partly mediated by microbiome-derived short-chain fatty acid signaling and altered vagal afferent tone [24]. Ring's 2025 *American Journal of Medicine* integrative review of HPA axis dysfunction lists gut health, immune system interactions, inflammation, and toxins among the principal upstream modifiers of cortisol rhythmicity, and explicitly identifies adaptogenic herbs as one of the therapeutic options operating along these axes [25].

The implication is that ashwagandha and *Rhodiola* may be best understood not as pharmacologic agents acting on central HPA circuitry but as multi-system biological modifiers whose central effects are partly downstream of microbiome-mediated peripheral changes. This further weakens any clinical model that uses serum cortisol as a sole proxy for adaptogenic effect, and it brings the gut-brain axis into the same explanatory frame that, in Part II, will accommodate the oxytocinergic effects of the human-animal bond.

3.5 The ashwagandha safety crisis

The clinical case for ashwagandha must now be made against an increasingly assertive international regulatory background. The Technical University of Denmark's 2020 risk assessment, building on a more cautious 2008 review, concluded that on the available data no safe lower limit of intake could be established, citing concerns about thyroid hormones, sex hormones, reproductive toxicity, and abortifacient use [9,10,13]. In April 2023 the Danish Veterinary and Food Administration removed ashwagandha from approved food supplements, and the country used the EU Rapid Alert System for Food and Feed (RASFF) to flag products in other member states [10]. Subsequent national actions have followed: the Swedish Food Agency in September 2022 ruled that the Danish assessment was applicable in Sweden on a municipal case-by-case basis; the Dutch National Institute for Public Health and the Environment (RIVM) in March 2024 concluded that products on the Dutch market "may lead to adverse effects such as liver injury, thyrotoxicosis and suppression of the adrenal system in sensitive people"; the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) in 2024 recommended that pregnant or breastfeeding women, minors, and individuals with thyroid, liver, or heart conditions avoid the herb; and Poland has maintained since 2020 a 3-gram root-powder cap with a 10-mg-withanolide ceiling and bans on use in children and pregnant women [11,13].

The Australian Therapeutic Goods Administration published a safety advisory in February 2024 [11]. In June 2024 the EU Heads of Food Safety Agencies Working Group on Food Supplements formally recommended prioritizing ashwagandha for an Article 8 procedure under Regulation (EC) No 1925/2006, citing "(potential) effects on reproduction, thyroid hormones, acetylcholinesterase, the immune system and due to liver toxicity. The toxicity data are limited and insufficient to derive a safe dose level or health-based guidance value" [11].

The clinical toxicology literature behind these actions is led by Philips and colleagues' 2023 *Hepatology Communications* case series — the first and largest from a single national context. Of twenty-three patients identified with ashwagandha-related liver injury at multiple Indian centers between January 2019 and December 2022, the authors reported in detail on eight patients with single-ingredient-formulation hepatotoxicity, predominantly male, with cholestatic hepatitis as the commonest presentation. Five had underlying chronic liver disease; three "presented with acute-on-chronic liver failure, and all 3 died on follow-up" [12]. Bokan and colleagues' 2023 *Pharmaceuticals* causality assessment using the updated Roussel Uclaf Causality Assessment Method (RUCAM) concluded that ashwagandha is "an emerging cause" of herb-induced liver injury [26]. The WHO VigiBase signal includes more than fifteen hepatobiliary reports specifically tied to *Withania somnifera*, and the cumulative national-authority adverse-event total exceeds seventy across all categories [11,13].

A 2025 *Frontiers in Nutrition* paper by Ronen and colleagues offers the most comprehensive AI-driven safety re-analysis to date [27]. Combining a natural language processing literature review (in which GPT-4 outperformed GPT-3.5 Turbo and SciBERT) with quantitative structure-activity relationship (QSAR) based toxicity prediction at the molecular level, the authors concluded that "the root of *Withania somnifera* (Ashwagandha) demonstrates a

favorable safety profile, particularly concerning liver and reproductive toxicity, when compared to other herbal supplements" — but only when root preparations are properly distinguished from non-root plant parts, whose toxicity potential is meaningfully higher. The careful reader will note that the authors are affiliated with a commercial entity (MeNow Ltd.), and that QSAR methods have well-known limitations for complex botanical mixtures, but the paper crystallizes a methodological problem that the broader regulatory literature has begun to acknowledge: the Danish DTU assessment did not consistently distinguish between root and aerial parts of the plant, and the cascading regulatory response has therefore been calibrated against an evidence base that may overestimate the risk from properly-prepared root extracts.

What is not in dispute is that the cumulative safety signal is large enough to warrant substantive revision of how the herb is positioned in naturopathic practice. A botanical that triggers continental-scale regulatory review, generates a documented hepatotoxicity case series with deaths in vulnerable patients, and is contraindicated in pregnancy, lactation, pediatric, thyroid, hepatic, and cardiac populations is no longer a first-line agent under the naturopathic principle of *primum non nocere*. It may remain a useful second-line agent in carefully selected patients, but the days of routine over-the-counter use, particularly without baseline and follow-up liver function monitoring, are — or should be — over.

This is the inflection point at which the human-animal bond literature becomes naturopathically relevant.

PART II: THE HUMAN-ANIMAL BOND AS ENDOGENOUS STRESS MODULATOR

4. Service Dog Partnerships as Measurable HPA Axis Interventions

4.1 The cortisol awakening response: a primer

The cortisol awakening response (CAR) is the rapid rise in salivary cortisol observed within the first thirty to forty-five minutes of morning awakening. Following the foundational work of Pruessner, Wüst, Hellhammer, Kirschbaum, and colleagues in the late 1990s, the CAR has emerged as the most clinically useful single marker of HPA axis integrity available in field research [28,29]. Approximately 75% of healthy adults demonstrate a mean cortisol increase of about 50% within the first thirty minutes after awakening, with peak elevations of 50–75% (and in some normative cohorts as high as 160%) within the first thirty to forty-five minutes [28,29,30]. The 2022 Stalder consensus guidelines codified the methodological standards for CAR assessment in the field [30]. Critically, the CAR requires no laboratory stressor, captures HPA reactivity rather than basal output, and is reliably altered in chronic stress, burnout, depression, and posttraumatic stress disorder. In healthy adults the response is robust; in PTSD it is characteristically blunted, reflecting the hyperarousal-induced dysregulation of HPA activity that yields atypical cortisol profiles [14,15].

4.2 The Purdue/Arizona cortisol awakening response program

The research program led by Rodriguez, Nieforth, and O'Haire — initially at Purdue's Center for the Human-Animal Bond and continuing at the University of Arizona College of Veterinary Medicine — has produced what is, to my knowledge, the only sustained physiological program documenting how the service dog partnership modifies the CAR. The initial 2018 *Psychoneuroendocrinology* cross-sectional study (n=73 veterans, 45 with a service dog and 28 on the waitlist) reported that the presence of a service dog was specifically associated with a larger magnitude awakening response, though not with waking cortisol values per se [15].

The 2024 *Scientific Reports* longitudinal clinical trial (NCT03245814) — frequently cited as "Nieforth et al. 2024" but operationally a Rodriguez–Nieforth–O'Haire collaboration with the Institute for Interdisciplinary Salivary Bioscience Research and Johns Hopkins University School of Medicine — represents the next-generation evidence [14]. The study assessed the cortisol awakening response for 245 participants at baseline and three-month follow-up across an intervention group (service dog: veterans n=88, partners n=46) and a control group (usual care: n=73, partners n=38). A total of 3,951 salivary samples were collected via passive drool immediately upon waking, at thirty minutes post-waking, and at forty-five minutes post-waking, across the two assessment days. Mixed-model repeated-measures (MMRM) analysis with multiple imputation by chained equations indicated that "veterans with a service dog had a significantly higher CAR in comparison to the usual care group ... Both the area under the curve with respect to increase (AUCi, $\beta = 1.46$, SE = 0.73, $p = 0.046$) and the absolute increase (AINC, $\beta = 0.05$, SE = 0.02, $p = 0.035$) were significantly higher at follow up when controlling for baseline values" [14]. The effect was specific to the veteran handler; their non-handler partners did not show a statistically significant CAR shift (AUCi β=1.36, p=0.255; AINC β=0.04, p=0.314), supporting the inference that the physiological effect is bond-specific rather than household-ambient.

This is, mechanistically, the cleanest evidence in the human-animal interaction literature for a measurable HPA axis intervention. The intervention — placement with a trained psychiatric assistance dog — is operationalized in a way that maps directly onto naturopathic clinical practice in a way that an isolated phytochemical does not.

4.3 The oxytocin-gaze loop and downstream HPA attenuation

The mechanistic candidate that ties the CAR findings to a broader literature is the oxytocinergic system. Nagasawa and colleagues' 2015 *Science* paper documented that thirty minutes of human-dog interaction produced increases in urinary oxytocin in both species when the dyad engaged in long mutual gaze, and that this effect was species-specific: "gazing behavior from dogs, but not wolves, increased urinary oxytocin concentrations in owners, which consequently facilitated owners' affiliation and increased oxytocin concentration in dogs" [16]. The paper has been the subject of methodological commentary, particularly regarding the inference of co-evolution from cross-species comparison [31], but the core finding — that gaze duration predicts oxytocin change in both members of a human-dog dyad — has held up across replication and extension.

Gnanadesikan and colleagues' 2024 *Psychoneuroendocrinology* study extended the paradigm to children (n=55, aged 8–10 years) interacting with their own pet dogs, with unfamiliar dogs, and in a nonsocial control condition, with concurrent measurement of both salivary and urinary oxytocin and oxytocin receptor gene (OXTR) methylation [18]. Children's oxytocin response was greater following dog interaction than nonsocial play, was similar with pet and unfamiliar dogs, and was associated with OXTR methylation patterns; pet dogs themselves showed increased salivary oxytocin during interaction. The Gnanadesikan paper is particularly important because it documents that the oxytocinergic response is not narrowly dependent on long-term familiarity — interaction with an unfamiliar but well-socialized dog is sufficient to mobilize the system in children. This finding has significant clinical implications for the deployment of trained therapy and service animals in patient populations without long-standing pet ownership.

The link from oxytocin to HPA axis attenuation is well established outside the human-animal interaction literature. Oxytocin released within the paraventricular nucleus of the hypothalamus exerts a tonic inhibitory effect on basal HPA axis activity by impairing CREB binding to the promoter region of the CRH gene, thereby reducing CRH transcription [32]. Oxytocinergic projections from the supraoptic and paraventricular nuclei reach corticotropin-releasing hormone neurons within the PVN itself, the anterior pituitary, the locus coeruleus, the amygdala, and the bed nucleus of the stria terminalis, with the integrated consequence of dampened noradrenergic stimulation of CRH release, reduced amygdala reactivity to threat stimuli, and attenuated downstream ACTH and cortisol output [32,33]. Neumann and colleagues established in rodent work that intracerebral oxytocin antagonism in the PVN disinhibits basal ACTH secretion, providing direct mechanistic confirmation that endogenous oxytocin maintains a tonic brake on the HPA axis under unstressed conditions [33]. Intranasal oxytocin administration in humans attenuates anticipatory anxiety, subjective stress, and HPA axis activation in laboratory stress paradigms, and reduces right amygdala responsiveness to fearful, angry, and even happy faces under blinded administration [32,33].

In other words: when a service dog handler gazes at her dog, the oxytocin-gaze loop documented by Nagasawa is the proximate behavioral mechanism by which the central oxytocinergic system documented by the broader neuroendocrinology literature is recruited, and the cortisol awakening response normalization documented by the Purdue/Arizona group is the distal downstream consequence. This is not speculation; it is the integration of three separately-published peer-reviewed bodies of evidence onto a single neuroendocrine map.

4.4 Psychoneuroimmunological evidence

Beyond cortisol and oxytocin, the broader animal-assisted intervention literature documents converging effects on dopamine, β-endorphin, prolactin, and immune parameters. Hunjan and Reddy's 2024 *Biomedical and Pharmacology Journal* review articulates the psychoneuroimmunological case: positive physical interaction with a therapy animal reduces stress, anxiety, depressive symptoms, aggressive tendencies, and cardiovascular reactivity, with measurable changes in dopaminergic reward signaling, endorphin release, prolactin secretion, and inflammatory cytokine balance [34]. Beetz and colleagues' 2012 *Frontiers in Psychology* review of sixty-nine original peer-reviewed studies remains the canonical synthesis, concluding that "the activation of the oxytocin system plays a key role in the majority of these reported psychological and psychophysiological effects of HAI" [17]. Documented effects span social attention, interpersonal behavior, mood, cortisol, heart rate, blood pressure, self-reported fear and anxiety, and cardiovascular morbidity. Beetz and colleagues specifically note that within the cortisol literature, the cortisol awakening response in one family-based study dropped from 58% to 10% in the morning when a dog was present in the family and rebounded to 48% upon the dog's removal — an early observational anticipation of what the Purdue/Arizona experimental program would later establish more rigorously [17].

4.5 The vision-impaired guide dog handler population: a critical research gap

It is at this point in the analysis that my positionality as a service dog trainer with specialized work in vision-impaired canine populations becomes analytically consequential. The published service dog physiology literature is concentrated almost entirely on two populations: psychiatric assistance dogs for veterans with PTSD (the Rodriguez/Nieforth/O'Haire program and a small number of independent replications) and, more broadly, mobility and medical service dogs. Guide dogs for the vision-impaired — the oldest and most institutionally developed category of

working dog placement, with established training schools dating to the 1920s and tens of thousands of active placements globally — have, to my knowledge, no published physiological stress biomarker studies. The available literature on this population consists almost entirely of self-report quality-of-life and psychosocial benefit data, including Whitmarsh's 2005 telephone survey of more than 800 visually impaired persons documenting independence, confidence, companionship, and social interaction as the principal reported benefits of guide dog ownership [35], and the 2021 *Frontiers in Veterinary Science* qualitative analysis of partnership endings by Nicholson and colleagues [36]. Even the Scandinavian first-time handler studies and the Austrian quality-of-life work cite psychosocial and subjective endpoints exclusively [37,38].

This is, methodologically, an extraordinary gap. The vision-impaired guide dog handler is, in effect, a natural experiment for the bond-based adaptogenic hypothesis. Unlike the PTSD veteran population, the guide dog handler does not have a baseline psychiatric pathology that confounds HPA axis measurement. Unlike the pet-owner literature, the guide dog dyad involves a uniquely intensive, mutually trained, daily life-and-mobility interdependence that is operationally closer to the "bonded pair" the oxytocin-gaze literature implicitly idealizes than any other human-animal relationship in routine clinical observation. Unlike the mobility service dog literature, the guide dog handler has a chronic baseline environmental stressor — navigating an environment without sight — whose physiological signature should, on first principles, be among the most sensitive available indicators of whether the dog partnership genuinely buffers HPA reactivity. And unlike emotional support animals, the guide dog is a formally trained, professionally placed, behaviorally tested working dog whose role admits of objective specification.

The absence of cortisol awakening response, salivary oxytocin, or even basic diurnal cortisol data in this population is the single most consequential empirical gap in the human-animal bond literature. I will return to this gap in Part III and in the Future Research Directions section, where I outline what such a study would look like.

PART III: CONVERGENCE AND THE NATUROPATHIC FRAMEWORK

5. Mechanistic Convergence: Two Paths to the Same HPA Axis

The substantive claim of this paper is that botanical adaptogens and the human-animal bond converge on a single neuroendocrine target — the corticotropin-releasing hormone neuron of the paraventricular nucleus and its downstream axis — through overlapping but distinct biochemical cascades. The five-dimension comparative framework introduced in Section 2.2 maps the convergence as follows.

Mechanism. Botanical adaptogens act, in the network pharmacology framework, by inducing low-magnitude stress-protective changes across Hsp70 and Hsp25, neuropeptide Y, NF-κB, FOXO3/DAF-16, nitric oxide, and stress-activated protein kinase signaling, with consequent effects on the responsiveness of the HPA axis to acute stressors [4,5,6]. The human-animal bond acts, in the oxytocin framework, through gaze-mediated activation of the central oxytocinergic system, with consequent inhibition of CRH gene transcription in the PVN, dampening of locus coeruleus noradrenergic input, and attenuation of amygdala threat reactivity [16,17,32,33]. Both pathways converge on reduced CRH release and on a normalized rather than maximized cortisol profile. Crucially, both share the polyvalent rather than single-target character: neither acts on one receptor; both act across an integrated neuroendocrine-immune network. The botanical achieves this through small effects at many molecular sites; the bond

achieves this through small effects at many behavioral and neural sites. The architecture of the action — polyvalent, distributed, contextually reversible — is shared.

Biomarker evidence. Both literatures report cortisol-modulating effects in placebo-controlled trials, with effect sizes that are comparable in order of magnitude: Albalawi's pooled −1.16 μg/dL for ashwagandha [7] and the Nieforth/Rodriguez/O'Haire AUCi β=1.46 (SE=0.73) for service dogs [14] are not directly commensurable but are both clinically meaningful. Both literatures also have methodological tension between physiological markers and subjective endpoints: ashwagandha's cortisol-perception disconnect is mirrored, in mirror image, by the human-animal bond literature's frequent observation that subjective bond strength predicts physiological effect more reliably than objective dyad characteristics do [17,18,34]. Where the literatures diverge is in their secondary biomarker base: oxytocin is well-studied in human-animal interaction and underdeveloped in adaptogenic medicine, while Hsp70 and FOXO3 are well-studied in adaptogenic medicine and untested in human-animal interaction. The integration of these biomarker programs — Hsp70 and oxytocin assayed in the same trial — would be a significant methodological advance.

Onset and duration. Adaptogens are typically dosed over 30 to 90 days for stress endpoints, with measurable cortisol effects emerging within four to eight weeks [7,8]. Service dog placement effects on the CAR are measurable at three months [14] but are likely to accumulate over the working life of the partnership (typically eight to twelve years for a guide dog). The acute oxytocin response to interaction is measurable within thirty minutes of intentional interaction [16,18]; the chronic adaptation, plausibly, takes months to years and persists for the duration of the bond. Critically, the bond is not metabolized, eliminated, or down-regulated as a pharmacological dose would be — there is no analog to tachyphylaxis. If

anything, the evidence suggests that bond strength deepens over years, and the physiological effect with it, until the loss of the dog produces a documented bereavement-and-mobility-loss syndrome with measurable psychosocial sequelae [36].

Safety profile. This is the most asymmetric dimension of the comparison. Botanical adaptogens, and ashwagandha in particular, have a hepatotoxicity signal substantial enough to have triggered the Danish ban, the EU Article 8 prioritization, the Philips et al. case series with three deaths in single-ingredient acute-on-chronic liver failure presentations, and explicit contraindications in pregnancy, lactation, pediatric, thyroid, hepatic, and cardiac populations [9,10,11,12,13]. The human-animal bond has no analogous toxicity signal. The relevant risks — allergy, zoonotic infection, injury — are operationally managed and, in well-trained dyads with appropriate veterinary oversight, are rare. The cost of bond-based intervention is logistical and financial (training, placement, lifetime care) rather than physiological. From a strict *primum non nocere* perspective, the bond clears the bar that ashwagandha is now, demonstrably, struggling to clear.

Alignment with naturopathic principles. Both interventions fit within the naturopathic framework, but they fit at different levels. Adaptogens implement *primum non nocere* (with the caveats just noted), the use of low-force natural substances, and — when properly used — treat the cause by modulating the stress response rather than suppressing symptoms. The human-animal bond, however, instantiates *vis medicatrix naturae* in a more direct sense: it is not a substance introduced into the organism, but the activation of an endogenous neuroendocrine system — oxytocinergic, vagal, behavioral — that the organism already possesses. The bond does not deliver healing; it elicits healing.

6. The Service Dog as Living Adaptogen: A Naturopathic Reframing

The central thesis of this paper can now be stated in its strongest form. *The service dog partnership is functionally an adaptogen* — a stress-response modifier that increases the organism's nonspecific resistance to stress by increasing its ability to adapt and survive, to use Panossian's 2017 definition [5] — and it is, more specifically, an *endogenous* adaptogen, one that acts not by introducing a phytochemical into the system but by recruiting the system's own oxytocinergic, behavioral, and HPA-modulatory capacities through an evolved interspecies relationship.

This framing has three implications.

First, the service dog partnership is the most direct contemporary expression of *vis medicatrix naturae* in stress medicine. Lindlahr's 1918 formulation — "this supreme power and intelligence, acting in and through every atom, molecule and cell in the human body, which is the true healer, the *vis medicatrix naturae*, which always endeavours to repair, to heal and to restore obstructions and to establish normal conditions within and around the patient" [39] — describes the healing capacity inherent in the organism. The botanical adaptogen supports that capacity by chemical means. The bond activates it by relational means. Of the two, the bond is closer to the original vitalist intuition because it does not require the introduction of any external agent into the body; it merely activates an evolved capacity the organism already possesses for interspecies social regulation. Logan and Selhub's 2012 *BioPsychoSocial Medicine* reframing of *vis medicatrix naturae* — explicitly extending the principle from internal healing response to "mindful contact with the animate and inanimate natural portions of the outdoor environment" [2] — provides the conceptual bridge. The service dog is the most evolved possible expression of "animate contact" available to a contemporary patient.

Second, the framing dissolves the cortisol-perception disconnect identified by Albalawi. If the felt sense of being supported is canonically produced by oxytocinergic social interaction, and if the Perceived Stress Scale measures (precisely) the felt sense rather than the cortisol value, then it should not be surprising that a pharmacological intervention acting on Hsp70, NPY, and steroid signaling reduces cortisol without reliably moving the PSS. The PSS is measuring the dimension that the bond-based intervention targets, not the dimension that the botanical targets. The integrated naturopathic clinical model that follows from this observation is one in which the botanical and the bond are not competitors but complements: ashwagandha or *Rhodiola* in carefully-selected patients modulates the physiological substrate; the human-animal bond, where clinically appropriate, modulates the perceptual and behavioral substrate. Both are required if both endpoints — cortisol *and* perceived stress — are to move together.

Third, the framing reorders the naturopathic safety calculation. Under *primum non nocere*, a first-line agent should have the lowest plausible harm profile compatible with efficacy. On current evidence, the human-animal bond meets that standard more cleanly than ashwagandha does. Where a patient has access to a service or assistance dog placement, where the patient population can safely bond (i.e., where there is no severe animal phobia, no immunocompromising condition incompatible with animal contact, no logistical impossibility), and where the clinical indication is HPA axis dysregulation with a subjective stress component, the bond-based intervention is the more conservative choice. The botanical becomes an adjunct.

7. An Integrated Naturopathic Clinical Model

The model I propose has four levels.

Level 1 — Foundational assessment. Diurnal salivary cortisol with a CAR protocol (waking, +30 min, +45 min sampling, following the 2022 Stalder consensus methodology [30]),

Perceived Stress Scale, brief animal-interaction history (current pets, prior service or therapy animal contact, animal phobia screening), and standard naturopathic intake (sleep, diet, microbiome, inflammatory markers). The CAR–PSS pair is the diagnostic key: a blunted CAR with elevated PSS is the canonical HPA dysregulation pattern that bond-based intervention is most likely to address; an elevated CAR with elevated PSS suggests a different (acute hyperarousal) profile that may require different sequencing.

Level 2 — Bond-based intervention as first-line for eligible patients. Where a patient qualifies for and has access to a service or assistance dog, this is the first-line stress intervention. Where formal service dog placement is not indicated, structured therapy animal contact under credentialed handler supervision, or supported pet acquisition for patients without contraindications, are graded down from this primary tier. The cost of a service dog placement is substantial — typically tens of thousands of dollars to train and place a working dog — and access is unequally distributed; this is a real clinical limit, not an evasion. But the broader human-animal interaction literature [17,18,34] documents oxytocinergic and cortisol effects from less intensive forms of contact, which can be staged into a clinically realistic intervention even where formal placement is not available.

Level 3 — Adjunctive botanical adaptogen. Where the bond intervention is in place but the cortisol component remains elevated, or where bond-based intervention is contraindicated or inaccessible, a botanical adaptogen is indicated. Given the safety profile reviewed in Section 3.5, *Rhodiola rosea* (standardized SHR-5 or equivalent root extract, 200–600 mg/day) is the more conservative first choice for most adult patients [6,21]. *Withania somnifera* root extract (KSM-66 or equivalent, 300–600 mg/day) remains a defensible option for patients without hepatic, thyroid, reproductive, or pregnancy contraindications, after informed consent regarding the regulatory

and case-series safety signals reviewed in Section 3.5 [7,8,11,12,13,27]. Baseline and 8–12 week liver function testing is prudent for any patient on ashwagandha for more than thirty days.

Level 4 — Foundational integrative care. Sleep, dietary modification (Mediterranean-pattern with attention to fermentable fiber for microbiome support), moderate exercise, mindfulness, and removal of obstacles to cure, in the sequence advanced by Ring's 2025 integrative HPA review [25]. These are not optional; they are the substrate without which neither bond nor botanical produces durable effect.

This model is proposed, not validated; Section 10 acknowledges its limitations.

8. Implications for Practitioner Training, Clinical Assessment, and Treatment Planning

Three implications for the field follow from the analysis advanced here.

Training. Naturopathic curricula currently treat botanical pharmacology as a core stress-medicine competency and the human-animal bond, if at all, as a topic in environmental medicine or "lifestyle." The argument advanced here suggests this ordering is no longer defensible. The human-animal bond should be a core competency, taught with the same rigor as adaptogenic pharmacology, with specific attention to (a) the psychoneuroendocrinology of oxytocin and its downstream HPA effects; (b) the assessment of bond strength as a clinical variable; (c) the appropriate referral pathways for service and therapy animal placement, including the legal and operational distinctions between service dogs, therapy animals, and emotional support animals; and (d) the contraindications and risks (phobia, allergy, immunocompromise, household feasibility, financial sustainability) that must be screened. Practitioners with significant patient populations who could benefit from bond-based

intervention should be expected to maintain professional relationships with established service and guide dog training organizations.

Clinical assessment. Standard naturopathic intake should include an animal-interaction history of sufficient depth to identify candidates for bond-based intervention and to characterize the existing bond context of patients with current animals. Brief validated instruments exist — the Monash Dog Owner Relationship Scale, the Lexington Attachment to Pets Scale, the Pet Attachment Questionnaire — and their incorporation into naturopathic intake is overdue. Where physiological assessment is feasible, the CAR protocol described in Level 1 above should be considered for any patient presenting with chronic stress, fatigue, insomnia, or unexplained inflammatory symptoms, in line with the 2022 Stalder consensus methodology [30].

Treatment planning. The clinical question should no longer be "which adaptogen?" but "which adaptogenic system?" The botanical is one such system; the bond is another. Sequencing, combination, and monitoring should reflect both. The presumption that botanical intervention is the default and bond intervention is the exotic adjunct is, on the current evidence, exactly inverted.

9. Where Bond-Based Interventions May Be Preferred

The conservative-institutionalist case for bond-first sequencing rests on three independent considerations.

First, the safety asymmetry is real and large. The EU Heads of Food Safety Agencies' June 2024 prioritization of ashwagandha for Article 8 review, the Philips and colleagues' case series with three deaths, and the cumulative VigiBase signal are not artifacts of a hostile regulatory climate or of an industry-skeptic working group; they are the legitimate output of pharmacovigilance systems doing exactly what they are designed to do [11,12,13]. A

naturopathic profession that takes its own pharmacovigilance seriously cannot simply dismiss them. The *Frontiers in Nutrition* QSAR analysis [27] usefully refines the picture (root-only preparations are safer than non-root preparations, and the regulatory evidence base did not always distinguish the two), but it does not erase the picture.

Second, the cortisol-perception disconnect is a structural feature of the botanical pathway, not a methodological bug to be fixed by larger trials. If the goal of stress medicine is to reduce both physiological dysregulation and perceived stress — and naturopathic medicine, with its commitment to treating the whole person, is committed to both — then an intervention that moves both endpoints together is preferable to one that moves only the first.

Third, the bond is more naturopathic. It does no harm; it elicits the body's own healing; it treats the cause (insufficient social-affiliative input to a stress-buffering system that evolved to be socially regulated); it treats the whole person; it operates preventively across the working life of the partnership; the practitioner functions as teacher rather than dispenser; and it is, in the deepest sense, the activation of *vis medicatrix naturae* rather than its supplementation. On every one of the seven foundational naturopathic principles, the bond-based intervention is a cleaner fit than ashwagandha at current evidence.

This is not a romantic claim; it is a clinical and regulatory one. The botanical that the field has positioned as its premier stress-management agent has, in the past three years, been banned in one EU member state, prioritized for restrictive review in the EU as a whole, contraindicated in five distinct vulnerable populations by national authorities, and implicated in fatal acute-on-chronic liver failure cases in a published clinical series. The bond has been associated with a normalized cortisol awakening response in the largest controlled trial of its kind. The asymmetry is not subtle.

10. Discussion

The three original contributions of this paper can now be evaluated.

10.1 First contribution: The human-animal bond as vis medicatrix naturae

The framing of the service dog partnership as a naturopathic stress intervention operating through *vis medicatrix naturae* is, to my knowledge, the first published statement of this thesis. Logan and Selhub's 2012 reframing of *vis medicatrix naturae* to include "mindful contact with the animate and inanimate natural portions of the outdoor environment" [2] opened the conceptual door, but did not walk through it to the interspecies bond. The Hunjan and Reddy 2024 psychoneuroimmunological synthesis [34] documented the relevant neuroendocrine effects without using the naturopathic vocabulary. The Purdue/Arizona group has produced the rigorous physiological evidence [14,15] but does not, in its publications, position the work within naturopathic theory. This paper performs the synthesis. The conceptual payoff is significant: it relocates the human-animal bond from the periphery of integrative medicine ("a nice supplement to the real interventions") to the center of naturopathic stress medicine ("the most direct contemporary expression of the foundational principle"). Practitioners should expect this reframing to be controversial precisely because it is novel; but the underlying evidence map presented in Parts I and II is, I argue, sufficiently robust to bear the conceptual weight.

10.2 Second contribution: Cortisol over-reliance as a structural problem

The comparative mechanistic analysis advanced in Sections 3–5 reveals that the field's reliance on cortisol as the sole marker of adaptogenic efficacy is no longer defensible. Albalawi's 2025 meta-analysis is the smoking gun [7]: a robust cortisol effect with a null PSS effect, in a botanical with thousands of years of empirical use as a stress agent, demands an explanation that

goes beyond the physiology of glucocorticoids. The explanation offered here — that perceived stress is regulated by an oxytocinergic-social-affiliative system that botanical adaptogens do not directly target, and that the bond-based intervention does directly target — is testable and, I argue, parsimonious. The implication for trial design is significant: adaptogen trials should include oxytocin and bond-related measures as covariates, not because the herb operates on oxytocin (it largely does not) but because the patient's oxytocinergic context will moderate the herb's apparent efficacy on subjective endpoints. Network-pharmacological mechanism, in other words, demands network-phenomenological measurement.

10.3 Third contribution: Vision-impaired guide dog handlers as a research agenda

The identification of the vision-impaired guide dog handler population as a critical research gap is, methodologically, the most concrete contribution of this paper. Section 4.5 argues that this population is in effect a natural experiment for the bond-based adaptogenic hypothesis, for reasons that include (a) the absence of baseline psychiatric pathology that confounds PTSD-population work, (b) the operationally exceptional intensity and duration of the partnership, (c) the chronic environmental stressor of navigating without sight, and (d) the well-established institutional infrastructure that makes recruitment and longitudinal follow-up tractable. A clinical trial in this population, designed along the lines of the 2024 Nieforth/Rodriguez/O'Haire protocol [14] but applied to guide dog placement rather than psychiatric assistance dog placement, would constitute the cleanest available test of the central thesis advanced here.

11. Limitations

Several limitations must be acknowledged.

This paper is a literature-based comparative analysis, not a meta-analysis, and not a clinical trial. The integrated clinical model proposed in Section 7 is theoretically derived and clinically informed but has not been prospectively tested. Sequencing and dosing recommendations represent the author's synthesis of the available evidence and should be applied with the standard cautions appropriate to any unvalidated model.

There are no published direct head-to-head trials comparing botanical adaptogens and service dog partnerships on HPA axis markers. The mechanistic convergence argued in Sections 5 and 6 is therefore an inference from independent literatures rather than from a single experimental design. The Future Research Directions section addresses this gap explicitly.

The Albalawi 2025 meta-analysis [7] reports moderate heterogeneity (I^2=50.9%) across the cortisol-reporting studies and includes only seven cortisol-reporting and six PSS-reporting trials (n=488 total); the cortisol-perception disconnect, while striking, is itself based on a modest evidence base. The Arumugam 2024 meta-analysis [8] reaches a different conclusion on PSS, suggesting that the disconnect may be more pronounced in some study subsets than in others. The interpretation advanced here weighs Albalawi as more methodologically conservative — its inclusion criteria are restrictive and its Cochrane Risk of Bias 2 application is fully reported — but does not claim that the disconnect is universal across all formulations, doses, or populations.

The author's positionality as a service dog trainer with vision-impaired specialization may introduce favorable bias toward bond-based interventions. The argument for safety asymmetry in Section 9 rests on regulatory and clinical-toxicology data that would survive review by an investigator with no animal-handling background, but the synthesizing framing — that the bond is more naturopathic than the herb on every one of the seven principles — is an argument that the

author's clinical perspective makes available, and that another author with a different background might frame differently.

The Ronen and colleagues 2025 *Frontiers in Nutrition* QSAR safety re-analysis [27] is authored by employees of a commercial entity (MeNow Ltd.), which is disclosed in the cited paper and noted here. The conclusion drawn from that paper in Section 3.5 — that the regulatory picture may overestimate risk from properly-prepared root preparations — should be read in light of this potential conflict of interest. The author has weighed the conflict and judged the methodological points to remain useful, but readers may weigh them differently.

Finally, the integration of *vis medicatrix naturae* with contemporary neuroendocrinology requires translating across philosophical idioms that resist easy mapping. The argument advanced here treats vitalism as a heuristic that organizes clinical attention toward endogenous capacity, rather than as a metaphysical commitment about a non-physical "vital force." Practitioners who hold a stronger metaphysical vitalism may find the synthesis acceptable; those who reject vitalism entirely may find the framing unhelpful. The clinical implications are intended to stand independently of the philosophical framing, and a reader who substitutes "endogenous regulatory capacity" for "*vis medicatrix naturae*" throughout the paper will lose nothing of the empirical argument.

12. Future Research Directions

Four specific studies follow directly from the analysis advanced here.

Study 1: Physiological stress biomarkers in vision-impaired guide dog handlers. A prospective longitudinal study of vision-impaired adults placed with their first guide dog, with cortisol awakening response (waking, +30, +45 minutes), evening cortisol, salivary oxytocin, and validated quality-of-life and perceived stress measures collected at baseline (pre-placement),

at one month, three months, six months, and twelve months post-placement. A matched waitlist-control group, paralleling the 2024 Nieforth design [14], would establish the comparator. Target enrollment of n=100 per arm would achieve adequate power for a CAR AUCi effect size of comparable magnitude to that observed in the veteran PTSD trial. The study should be conducted in cooperation with established guide dog schools whose placement timelines and behavioral assessment protocols are standardized.

Study 2: Head-to-head trial of adaptogen versus service dog versus combined intervention. A four-arm randomized trial in adults with documented HPA axis dysregulation (defined by blunted CAR plus elevated PSS): (a) ashwagandha root extract 600 mg/day; (b) standardized service or assistance dog placement; (c) combined intervention; (d) wait-list / standard-of-care control. Primary endpoints: CAR AUCi at three and six months; PSS at three and six months. Secondary endpoints: salivary oxytocin, inflammatory cytokines (CRP, IL-6, TNF-α), sleep quality (PSQI), and quality of life. Liver function panels should be obtained at baseline, eight weeks, and six months for the botanical arms. This is the trial that the comparative argument in Section 5 most directly motivates and that the field needs in order to translate the integrated clinical model from theoretical proposal to evidence-based practice.

Study 3: Mechanistic studies of oxytocin downstream effects parallel to known adaptogen pathways. Do periods of high oxytocinergic activity (as indexed by salivary oxytocin during structured human-dog interaction) produce measurable changes in the Hsp70, neuropeptide Y, NF-κB, and FOXO3 signaling pathways that adaptogens target [4,5,6]? Are there shared transcriptional networks downstream of oxytocinergic and adaptogenic signaling? Microarray and proteomic analyses in peripheral blood mononuclear cells before and after defined interaction periods would address this question. The expected result — partial overlap of

the network response — would significantly strengthen the "living adaptogen" framing by providing molecular-level evidence that the two interventions converge on shared downstream transcriptional architecture.

Study 4: Secondary analysis of existing adaptogen trial datasets stratified by animal companionship. A re-analysis of existing ashwagandha and *Rhodiola* trial datasets, stratifying by participants' animal companionship status and bond strength at baseline, with PSS as the dependent variable. The hypothesis is that the cortisol-perception disconnect identified by Albalawi will be moderated by baseline animal-bond context: participants with strong existing animal bonds will show better PSS responses to adaptogenic treatment than those without. This study can be conducted from existing data without new recruitment, requiring only collaboration with the original investigators and access to participant-level demographic and lifestyle data.

13. Conclusion

This paper has argued that the service dog partnership is best understood within naturopathic theory as a *living adaptogen*: a stress-response modifier that increases the organism's nonspecific resistance to stress, that acts through a polyvalent rather than single-target neuroendocrine mechanism, and that does so as the most direct contemporary expression of *vis medicatrix naturae* available to clinical practice. The argument has rested on three pillars. The first is the empirical pressure on botanical adaptogens, expressed most clearly in the cortisol-perception disconnect documented by Albalawi 2025 (cortisol −1.16 μg/dL, $p<0.001$, but PSS $p=0.40$) and the ashwagandha safety crisis that has produced the April 2023 Danish ban, the June 2024 EU Heads of Food Safety Agencies Article 8 prioritization, and the Philips et al. 2023 case series with three deaths from single-ingredient acute-on-chronic liver failure. The second is the rigorous physiological evidence for the human-animal bond as a measurable HPA axis

intervention, anchored by the Nieforth/Rodriguez/O'Haire 2024 cortisol awakening response trial (n=245, AUCi β=1.46, SE=0.73, p=0.046) and supported by the Nagasawa 2015 oxytocin-gaze loop, the Gnanadesikan 2024 child-dog oxytocin findings, the Beetz 2012 sixty-nine-study review, and the Hunjan and Reddy 2024 psychoneuroimmunological synthesis. The third is the alignment of the bond-based intervention with all seven foundational naturopathic principles, an alignment that the botanical, on current safety evidence, no longer cleanly achieves.

The paradigm expansion this paper proposes is modest in its claims and considerable in its consequences. It does not displace botanical adaptogens; it relocates them within an integrated model in which the bond comes first. It does not romanticize the human-animal bond; it asks the field to take seriously the rigorous physiological evidence that the bond-based literature has produced and that the naturopathic literature has, until now, not engaged. And it identifies an unstudied population — vision-impaired guide dog handlers — whose physiological response to placement could, within a small number of well-designed studies, establish the bond-as-adaptogen framing on a footing as solid as that on which the ashwagandha literature now rests.

The principle of *vis medicatrix naturae* has, since Hippocrates, named the conviction that healing arises from within the organism and that the physician's task is to remove obstacles to that healing. Naturopathic medicine has spent a century deploying botanical agents in service of that conviction. The argument of this paper is that the next century should add to that deployment the recognition that the therapeutic bond between humans and dogs — a relationship that evolved over roughly fifteen thousand years of co-domestication and that recruits the oldest social-regulatory systems in the mammalian repertoire — is itself a legitimate, measurable, and

clinically significant naturopathic intervention. The service dog is not a metaphor for an adaptogen. The service dog *is* an adaptogen.

References

[1] World Naturopathic Federation. Naturopathic Principle: Healing Power of Nature (*vis medicatrix naturae*). White Paper. Toronto: World Naturopathic Federation; 2017.

[2] Logan AC, Selhub EM. *Vis medicatrix naturae*: does nature "minister to the mind"? *BioPsychoSocial Medicine*. 2012;6:11.

[3] Brekhman II, Dardymov IV. New substances of plant origin which increase nonspecific resistance. *Annual Review of Pharmacology*. 1969;9(1):419–430.

[4] Panossian A, Lemerond T, Efferth T. Two Sides of the Same Coin for Health: Adaptogenic Botanicals as Nutraceuticals for Nutrition and Pharmaceuticals in Medicine. *Pharmaceuticals*. 2025;18(9):1346.

[5] Panossian A. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. *Annals of the New York Academy of Sciences*. 2017;1401(1):49–64.

[6] Panossian A, Wikman G. Effects of Adaptogens on the Central Nervous System and the Molecular Mechanisms Associated with Their Stress-Protective Activity. *Pharmaceuticals*. 2010;3(1):188–224.

[7] Albalawi AA. Dual impact of Ashwagandha: Significant cortisol reduction but no effects on perceived stress – A systematic review and meta-analysis. *Nutrition and Health*. 2025;31(4):1395–1408.

[8] Arumugam V, Vijayakumar V, Balakrishnan A, Bhandari RB, Boopalan D, Ponnurangam R, Sankaralingam Thirupathy V, Kuppusamy M. Effects of Ashwagandha (*Withania somnifera*) on stress and anxiety: A systematic review and meta-analysis. *Explore (NY)*. 2024;20(6):103062.

[9] Technical University of Denmark (DTU) National Food Institute. Risk assessment of *Withania somnifera* (Ashwagandha) for use in food supplements. Copenhagen: DTU; 2020.

[10] Danish Veterinary and Food Administration (Fødevarestyrelsen). Notice on ashwagandha in food supplements. April 2023.

[11] EU Heads of Food Safety Agencies Working Group on Food Supplements. First Report on the Article 8 Procedure under Regulation (EC) No 1925/2006 for *Withania somnifera*. 6 June 2024.

[12] Philips CA, Valsan A, Theruvath AH, Ravindran R, Oommen TT, Rajesh S, Bishnu S, Augustine P; Liver Research Club India. Ashwagandha-induced liver injury — A case series from India and literature review. *Hepatology Communications*. 2023;7(10):e0270.

[13] Brendler T, Williamson EM. Ashwagandha: Is It Safe? Part 1: A Regulatory Review. *Phytotherapy Research*. 2025; (early view, doi:10.1002/ptr.70151).

[14] Nieforth LO, Rodriguez KE, Zhuang R, Miller EA, Sabbaghi A, Schwichtenberg AJ, Granger DA, O'Haire ME. The cortisol awakening response in a 3 month clinical trial of service dogs for veterans with posttraumatic stress disorder. *Scientific Reports*. 2024;14:1664.

[15] Rodriguez KE, Bryce CI, Granger DA, O'Haire ME. The effect of a service dog on salivary cortisol awakening response in a military population with posttraumatic stress disorder (PTSD). *Psychoneuroendocrinology*. 2018;98:202–210.

[16] Nagasawa M, Mitsui S, En S, Ohtani N, Ohta M, Sakuma Y, Onaka T, Mogi K, Kikusui T. Oxytocin-gaze positive loop and the coevolution of human-dog bonds. *Science*. 2015;348(6232):333–336.

[17] Beetz A, Uvnäs-Moberg K, Julius H, Kotrschal K. Psychosocial and psychophysiological effects of human-animal interactions: The possible role of oxytocin. *Frontiers in Psychology*. 2012;3:234.

[18] Gnanadesikan GE, King KM, Carranza E, Flyer AC, Ossello G, Smith PG, Steklis NG, Steklis HD, Carter CS, Connelly JJ, Barnett M, Gee N, Tecot SR, MacLean EL. Effects of human-animal interaction on salivary and urinary oxytocin in children and dogs. *Psychoneuroendocrinology*. 2024;169:107147.

[19] Bachour G, Samir A, Haddad S, Houssaini MA, El Radad M. Effects of Ashwagandha Supplements on Cortisol, Stress, and Anxiety Levels in Adults: A Systematic Review and Meta-Analysis. *BJPsych Open*. 2025;11(Suppl 1):S136.

[20] Pandit S, Srivastav AK, Sur TK, Chaudhuri S, Wang Y, Biswas TK. Effects of *Withania somnifera* Extract in Chronically Stressed Adults: A Randomized Controlled Trial. *Nutrients*. 2024;16(9):1293.

[21] Ishaque S, Shamseer L, Bukutu C, Vohra S. *Rhodiola rosea* for physical and mental fatigue: a systematic review. *BMC Complementary and Alternative Medicine*. 2012;12:70.

[22] Panossian A, Lemerond T, Efferth T. Adaptogens in Long-Lasting Brain Fatigue: An Insight from Systems Biology and Network Pharmacology. *Pharmaceuticals*. 2025;18(2):261.

[23] Bharani KK, Devarasetti AK, Bobbili R, Khurana A, Veera Hanuman DD, Gudepu R, Guda S. The role of Ashwagandha in modulating gut parameters in dogs — a randomized double-blind placebo-controlled trial. *Frontiers in Veterinary Science*. 2025;11:1491989.

[24] Psychobiotics and Adaptogens: A Systematic Review of Gut-Brain Axis Interventions for Stress, Mood, and Cognition. *Applied Sciences*. 2025;15(8):4564.

[25] Ring M. An Integrative Approach to HPA Axis Dysfunction: From Recognition to Recovery. *American Journal of Medicine*. 2025;138(10):1451–1463.

[26] Bokan G, Glamočanin T, Mavija Z, Vidović B, Stojanović A, Björnsson ES, Vučić V. Herb-Induced Liver Injury by Ayurvedic Ashwagandha as Assessed for Causality by the Updated RUCAM: An Emerging Cause. *Pharmaceuticals*. 2023;16(8):1129.

[27] Ronen Y, Ebert C, Tamim-Yecheskel B-C, Zev S, Kantor O, Ben-Hamo Arbel H. Comprehensive safety evaluation of *Withania somnifera* (Ashwagandha): an AI-driven meta-analysis and quantitative structure–activity relationship based toxicity assessment. *Frontiers in Nutrition*. 2025;12:1658265.

[28] Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, von Auer K, Jobst S, Kaspers F, Kirschbaum C. Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sciences*. 1997;61(26):2539–2549.

[29] Wüst S, Wolf J, Hellhammer DH, Federenko I, Schommer N, Kirschbaum C. The cortisol awakening response — normal values and confounds. *Noise and Health*. 2000;2(7):79–88.

[30] Stalder T, Lupien SJ, Kudielka BM, Adam EK, Pruessner JC, Wüst S, Dockray S, Smyth N, Evans P, Kirschbaum C, et al. Evaluation and update of the expert consensus guidelines for the assessment of the cortisol awakening response (CAR). *Psychoneuroendocrinology*. 2022;146:105946.

[31] Fiset S, Plourde V. Commentary: Oxytocin-Gaze Positive Loop and the Coevolution of Human-Dog Bonds. *Frontiers in Psychology*. 2015;6:1845.

[32] Selvaraj V. A short note on oxytocin and stress attenuation. *Bioinformation*. 2022;18(5):425–428.

[33] Neumann ID, Krömer SA, Toschi N, Ebner K. Brain oxytocin inhibits the (re)activity of the hypothalamo-pituitary-adrenal axis in male rats: involvement of hypothalamic and limbic brain regions. *Regulatory Peptides*. 2000;96(1–2):31–38.

[34] Hunjan UG, Reddy KJ. Psychoneuroimmunological Perspective of Animal-Assisted Therapy. *Biomedical and Pharmacology Journal*. 2024;17(3):1831–1836.

[35] Whitmarsh L. The benefits of guide dog ownership. *Visual Impairment Research*. 2005;7(1):27–42.

[36] Nicholson J, Kemp-Wheeler S, Griffiths D. The End of the Partnership With a Guide Dog: Emotional Responses, Effects on Quality of Life and Relationships With Subsequent Dogs. *Frontiers in Veterinary Science*. 2021;8:543463.

[37] Lloyd JKF, La Grow S, Stafford KJ, Budge RC. The Guide Dog as a Mobility Aid Part 2: Perceived Changes to Travel Habits. *International Journal of Orientation and Mobility*. 2008;1(1):34–45.

[38] Glenk LM, Přibylová L, Stetina BU, Demirel S, Weissenbacher K. Perceptions on Health Benefits of Guide Dog Ownership in an Austrian Population of Blind People with and without a Guide Dog. *Animals*. 2019;9(7):428.

[39] Lindlahr H. *Nature Cure: Philosophy and Practice Based on the Unity of Disease and Cure*. Chicago: Nature Cure Publishing; 1918.

[40] Panossian A, Efferth T. Network Pharmacology of Adaptogens in the Assessment of Their Pleiotropic Therapeutic Activity. *Pharmaceuticals*. 2022;15(9):1051.

[41] Olsson EMG, von Schéele B, Panossian A. A randomised, double-blind, placebo-controlled, parallel-group study of the standardised extract SHR-5 of the roots of *Rhodiola rosea* in the treatment of subjects with stress-related fatigue. *Planta Medica*. 2009;75(2):105–112.

[42] Akhgarjand C, Asoudeh F, Bagheri A, Kalantar Z, Vahabi Z, Shab-Bidar S, Rezvani H, Djafarian K. Does Ashwagandha supplementation have a beneficial effect on the management of anxiety and stress? A systematic review and meta-analysis of randomized controlled trials. *Phytotherapy Research*. 2022;36(11):4115–4124.

[43] Salve J, Pate S, Debnath K, Langade D. Adaptogenic and Anxiolytic Effects of Ashwagandha Root Extract in Healthy Adults: A Double-Blind, Randomized, Placebo-Controlled Clinical Study. *Cureus*. 2019;11(12):e6466.

[44] Lopresti AL, Smith SJ, Malvi H, Kodgule R. An investigation into the stress-relieving and pharmacological actions of an ashwagandha extract: A randomized, double-blind, placebo-controlled study. *Medicine (Baltimore)*. 2019;98(37):e17186.

[45] Hung SK, Perry R, Ernst E. The effectiveness and efficacy of *Rhodiola rosea* L.: A systematic review of randomized clinical trials. *Phytomedicine*. 2011;18(4):235–244.

[46] Pizzorno JE, Murray MT, editors. *Textbook of Natural Medicine*. 5th ed. St. Louis, MO: Elsevier; 2020.

[47] Yehuda R. Status of glucocorticoid alterations in post-traumatic stress disorder. *Annals of the New York Academy of Sciences*. 2009;1179:56–69.

[48] Chida Y, Steptoe A. Cortisol awakening response and psychosocial factors: A systematic review and meta-analysis. *Biological Psychology*. 2009;80(3):265–278.

[49] Adam EK, Quinn ME, Tavernier R, McQuillan MT, Dahlke KA, Gilbert KE. Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. *Psychoneuroendocrinology*. 2017;83:25–41.

[50] Uvnäs-Moberg K, Handlin L, Petersson M. Self-soothing behaviors with particular reference to oxytocin release induced by non-noxious sensory stimulation. *Frontiers in Psychology*. 2015;5:1529.

[51] Carter CS. Oxytocin pathways and the evolution of human behavior. *Annual Review of Psychology*. 2014;65:17–39.

[52] Olff M, Frijling JL, Kubzansky LD, Bradley B, Ellenbogen MA, Cardoso C, Bartz JA, Yee JR, van Zuiden M. The role of oxytocin in social bonding, stress regulation and mental health: an update on the moderating effects of context and interindividual differences. *Psychoneuroendocrinology*. 2013;38(9):1883–1894.

[53] Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry*. 2003;54(12):1389–1398.

[54] O'Haire ME, Rodriguez KE. Preliminary efficacy of service dogs as a complementary treatment for military veterans with posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*. 2018;86(2):179–188.

[55] Leighton SC, Rodriguez KE, Jensen CL, MacLean EL, Davis LW, Ashbeck EL, Bedrick EJ, O'Haire ME. Service Dogs for Veterans and Military Members With Posttraumatic Stress Disorder: A Nonrandomized Controlled Trial. *JAMA Network Open*. 2024;7(6):e2414686.

[56] Rodriguez KE, Greer J, Beck AM, O'Haire ME. The effects of assistance dogs on psychosocial health and wellbeing: A systematic literature review. *PLOS ONE*. 2020;15(12):e0243302.