

# Auto-somatic ReGenesis

## *Soma ReGenesis*

*Peganum Harmala Beta-Carboline Alkaloids: Mechanisms of Regeneration, Longevity, and the Kaya Kalpa Dark Retreat Hypothesis*

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*This summary was compiled from published peer-reviewed research and theoretical analysis. It is intended for researchers and does not constitute medical advice.*

## 1. Overview

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The seeds of *Peganum harmala* (Syrian rue) contain a complex of beta-carboline alkaloids—primarily harmine, harmaline, and tetrahydroharmine—that have been used in traditional medicine across the Middle East, Central Asia, and South America for centuries. Recent pharmacological research has revealed that these compounds simultaneously engage multiple biological pathways directly implicated in cellular aging, tissue regeneration, and longevity. This document summarizes the published evidence for these mechanisms and proposes a framework for their application in human regeneration—both as a daily low-dose protocol and within the context of extended dark retreat (kaya kalpa), an ancient practice documented in Ayurvedic, Siddha, and Taoist traditions.

## 2. The Alkaloid Profile of *Peganum Harmala* Seeds

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*Peganum harmala* seeds typically contain between 3–5% total beta-carboline alkaloids by dry weight, with harmaline generally predominating over harmine in the seed fraction. Multiple HPLC studies cluster in this range: the Asgarpanah comprehensive review reports total alkaloid content of 2–5%; a Chinese Academy of Sciences HPLC analysis found approximately 2.02% harmine and 2.87% harmaline (~4.9% total); a Euro-Mediterranean Journal study (2024) found 2.11% harmine and 2.38% harmaline (~4.5% total); and a separate antileishmanial study (PMC) measured 1.7% harmine and 3% harmaline (~4.7% total). Wikipedia’s summary of the literature cites “roughly 3%, though tests have documented anywhere from 2–7% or even higher.” One frequently cited study (Herraiz et al., 2010, *Food and Chemical Toxicology*) reported anomalously

high figures of 4.3% harmine and 5.6% harmaline (~10% total)—values substantially above the rest of the literature and likely reflecting either an exceptionally potent seed lot or methodological differences in extraction.

For practical purposes this document uses a working range of approximately 30–50mg of total alkaloids per gram of whole powdered seed, corresponding to 3–5% alkaloid content, with the understanding that actual content varies with source, growing conditions, and storage. This variability is a meaningful consideration for any protocol—seeds from different suppliers may deliver substantially different alkaloid loads per gram.

All three major alkaloids are reversible inhibitors of monoamine oxidase A (MAO-A) at sufficient doses. However, the regenerative and longevity-relevant properties discussed in this document operate through entirely different mechanisms—primarily DYRK1A kinase inhibition, mitochondrial protection, and stem/progenitor cell reactivation—which appear to activate at lower doses than those required for significant MAO inhibition.

### 3. Key Regenerative Mechanisms

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#### *3.1 DYRK1A Inhibition and Reactivation of Quiescent Progenitor Cells*

Dual-specificity tyrosine-regulated kinase 1A (DYRK1A) is a kinase that enforces cellular quiescence—it acts as a brake on cell division in adult tissues. In embryonic and neonatal development, rapid cell proliferation is the norm. As the organism matures, DYRK1A activity increases, holding progenitor and stem cell populations in a dormant, non-dividing state.

Harmine is a potent and selective inhibitor of DYRK1A. Research from Mount Sinai (Wang et al., 2015, *Nature Medicine*) demonstrated that harmine-mediated DYRK1A inhibition:

- ◆ Induced human pancreatic beta-cell proliferation—the first compound shown to reliably make adult human beta cells replicate
- ◆ Expanded beta-cell mass and improved glycemic control in diabetic mouse models
- ◆ Operated through the NFAT (Nuclear Factor of Activated T-cells) signaling pathway downstream of DYRK1A

Critically, harmine’s effects on beta cells went beyond mere proliferation. A 2023 study (*Diabetes*, American Diabetes Association) and a 2025 preprint (bioRxiv) showed that harmine uniquely drives both proliferation AND differentiation of beta cells simultaneously—a property not

shared by other DYRK1A inhibitors. This dual action was found to operate through an as-yet-unidentified secondary target involving protein kinase A (PKA) activation, distinct from the DYRK1A pathway.

The dose-response relationship follows a bell-shaped curve: moderate concentrations drive maximum proliferation, while excessive concentrations actually inhibit it. This finding was established in vitro at specific micromolar concentrations in cell culture. The translation of these concentrations to effective human oral doses has not been established—meaning the peak of the bell curve cannot currently be mapped with confidence onto a specific gram-weight of whole seed. This has important implications for dosing protocols, discussed in Section 6.

The DYRK1A inhibition mechanism is not tissue-specific in principle. While the most rigorous studies have been conducted in pancreatic beta cells and neural progenitors, DYRK1A is expressed throughout the body and regulates quiescence in multiple progenitor cell populations. This suggests that harmine’s proliferative effects may extend to resident stem and progenitor cells in bone, cartilage, liver, kidney, gut, and other tissues—though comprehensive mapping of tissue-specific responses has not yet been completed.

### 3.2 Neurogenesis

Research published in *Scientific Reports* demonstrated that harmine, tetrahydroharmine, and harmaline—all three major *Peganum harmala* alkaloids—stimulate adult neurogenesis in vitro. Using neurospheres prepared from progenitor cells obtained from the subventricular and subgranular zones of adult mouse brains, all compounds stimulated:

- ♦ Neural stem cell proliferation
- ♦ Migration of new neural cells
- ♦ Differentiation into functional adult neurons

This finding establishes that harmaline shares harmine’s neurogenic properties, and that the full alkaloid complex of *Peganum harmala*, not just the isolated harmine, drives neural regeneration. The researchers noted that modulation of brain plasticity could be a major mechanism underlying the antidepressant effects observed with these compounds.

A related beta-carboline, 9-methyl-beta-carboline, was shown to stimulate gene expression of several critical neurotrophic factors, including BDNF (brain-derived neurotrophic factor), and to increase ATP content in neuronal cells—directly linking beta-carbolines to both neuronal growth signaling and enhanced cellular energy production.

### 3.3 Mitochondrial Protection and Enhancement

Mitochondrial dysfunction is a central driver of aging and age-related disease. The beta-carboline alkaloids interact with mitochondria in a dose-dependent, biphasic manner that is critical to understand:

#### **At low to moderate doses (protective range):**

- ◆ Harmaline, harmalol, and harmine protected brain mitochondria against oxidative damage, reducing mitochondrial swelling and preserving membrane potential (Kim et al., 2001, *Journal of Neurochemistry*)
- ◆ Harmine increased mitochondrial complex I activity in the prefrontal cortex and complex IV activity in the striatum (Réus et al., 2012, *Depression Research and Treatment*)
- ◆ All three alkaloids attenuated MPP<sup>+</sup>-induced inhibition of mitochondrial electron flow and dopamine-induced thiol oxidation and carbonyl formation in mitochondria
- ◆ Beta-carbolines alone did not show significant cytotoxic effects on neuronal cells at protective concentrations
- ◆ The compounds scavenged reactive oxygen species (ROS) directly, reducing oxidative damage through radical-scavenging action and inhibition of thiol oxidation

#### **At high concentrations (inhibitory range):**

- ◆ Mitochondrial respiratory efficiency decreased in a concentration-dependent manner in isolated liver mitochondria at millimolar concentrations
- ◆ Harmine's cytotoxic effects were greater than harmaline's at equivalent high concentrations, suggesting harmaline has a wider therapeutic window

Importantly, a three-month chronic toxicity study in rats administered harmine at doses of 2.5 to 10 mg/kg/day found no toxic effects on morphological or histopathological examination at any dose level. For an 80kg human, this range corresponds to roughly 200–800mg of pure harmine daily—substantially higher than what is delivered by a regenerative-dose protocol using whole powdered seed.

### 3.4 Antioxidant and Anti-inflammatory Properties

Harmine reduces levels of inflammatory mediators, NADPH oxidase, reactive oxygen species, and inhibits acetylcholinesterase and butyrylcholinesterase. Harmine's antioxidant activity has been demonstrated to lower aggregation-induced elevation in oxidative stress in cellular models, directly addressing the oxidative damage that drives aging at the cellular level.

These anti-inflammatory and antioxidant properties are particularly relevant given that chronic low-grade inflammation ("inflammaging") is increasingly recognized as a central driver of age-related decline.

### 3.5 Musculoskeletal Regeneration: Bone, Cartilage, and Connective Tissue

Perhaps the most striking evidence for harmine's regenerative potential comes from musculoskeletal research, where harmine has been shown to simultaneously promote tissue building and prevent tissue breakdown across the entire skeletal system.

#### BONE REGENERATION

Harmine has a remarkable dual action on bone metabolism:

**Promoting bone formation (osteogenesis):** Research by Yonezawa et al. (2011, *Biochemical and Biophysical Research Communications*) demonstrated that harmine promotes osteoblast differentiation through the bone morphogenetic protein (BMP) signaling pathway. Specifically, harmine:

- ◆ Promoted alkaline phosphatase (ALP) activity—an early marker of osteoblast differentiation
- ◆ Increased expression of osteoblast marker genes ALP and Osteocalcin
- ◆ Enhanced mineralization of bone-forming cells
- ◆ Induced osteoblast differentiation in primary calvarial osteoblasts and mesenchymal stem cell lines
- ◆ Increased expression of BMP-2, BMP-4, BMP-6, and BMP-7—the key growth factors that drive bone formation
- ◆ Activated the transcription factors Runx2 and Osterix—the master regulators of osteoblast differentiation
- ◆ Activated both BMP-responsive and Runx2-responsive reporter genes

Structure-activity relationship studies revealed that the C3-C4 double bond and the 7-methoxy group of harmine were specifically important for its osteogenic activity.

**Preventing bone loss (anti-resorption):** The same research group had previously demonstrated that harmine inhibits osteoclast differentiation and bone resorption both in vitro and in vivo. Osteoclasts are the cells that break down bone tissue. By simultaneously stimulating bone-building osteoblasts and suppressing bone-destroying osteoclasts, harmine tips the entire balance of bone metabolism toward net bone formation.

The BMP signaling pathway that harmine activates is the same pathway responsible for bone formation during embryonic development. Harmine is essentially reactivating developmental bone-formation programs in adult cells—consistent with the broader pattern of developmental pathway reactivation seen across all of harmine’s regenerative effects.

The researchers concluded that harmine has bone anabolic effects and may be useful for the treatment of bone-decreasing diseases and bone regeneration. A 2023 review in *Bone Research* (Nature) confirmed these findings, noting that harmine induced osteoblast differentiation across multiple cell types by activating the BMP pathway and upregulating Runx2 gene expression.

#### CARTILAGE REGENERATION AND PROTECTION

Harmine demonstrates both chondrogenic (cartilage-forming) and chondroprotective (cartilage-preserving) effects:

A study published in PubMed (2012) screened a compound library specifically seeking molecules that could induce CCN2/CTGF (connective tissue growth factor) in chondrocytes. CCN2 has been established as having essential roles in cartilage development, chondrocyte proliferation and differentiation, and regulation of extracellular matrix metabolism. Prior studies had demonstrated that CCN2 can regenerate surgical defects in articular cartilage, and that transgenic mice overexpressing cartilage-specific CCN2 were more resistant to aging-related cartilage degradation.

From this library screen, harmine was identified as a novel inducer of CCN2 in both human chondrocytic cells and osteoarthritic articular chondrocytes. Harmine:

- ♦ Increased expression of aggrecan—the proteoglycan responsible for cartilage’s compressive resistance and water-retention capacity
- ♦ Increased expression of COL2 $\alpha$ 1 (type II collagen)—the primary structural protein of cartilage
- ♦ Induced CCN2/CTGF—the growth factor essential for cartilage development and repair

These are the two key molecules (aggrecan and type II collagen) that define functional hyaline cartilage—the type found in joints. Their upregulation by harmine suggests direct cartilage regenerative potential.

The study's title—"Novel chondrogenic and chondroprotective effects of the natural compound harmine"—explicitly identifies both the ability to form new cartilage and to protect existing cartilage from degradation.

#### **DYRK1A AND OSTEOARTHRITIS: PHARMACEUTICAL VALIDATION**

The pharmaceutical industry has independently validated the DYRK1A pathway as a target for musculoskeletal regeneration. Lorecivint, a drug that works through inhibition of CLK2 and DYRK1A—the same kinase target that harmine hits—has been developed as a potentially disease-modifying treatment for knee osteoarthritis and has progressed through clinical trials. This represents independent pharmaceutical validation that the mechanism harmine engages is considered therapeutically relevant for joint disease.

#### **THE COMPLETE MUSCULOSKELETAL PICTURE**

Taken together, the musculoskeletal research reveals that harmine:

1. Builds new bone by activating BMP signaling, Runx2, and Osterix
2. Prevents bone loss by inhibiting osteoclast differentiation
3. Promotes new cartilage formation by inducing CCN2/CTGF and increasing aggrecan and type II collagen
4. Protects existing cartilage from age-related and osteoarthritic degradation
5. Engages the DYRK1A pathway that pharmaceutical companies are independently pursuing for joint disease

This is particularly significant for the regenerative and longevity framework because musculoskeletal decline—loss of bone density, cartilage degradation, joint deterioration—is one of the most functionally limiting aspects of aging. A single natural compound complex that simultaneously addresses bone formation, bone preservation, cartilage regeneration, and cartilage protection represents a uniquely comprehensive approach to musculoskeletal aging.

In the context of the kaya kalpa dark retreat hypothesis, the musculoskeletal evidence is especially relevant to the traditional accounts of physical regeneration—including the restoration of structural tissues—reported in historical texts. The ability of harmine to reactivate developmental bone-formation programs (BMP signaling) in adult cells provides a pharmacological mechanism that could account for such observations.

## 4. Endogenous Beta-Carbolines: The Body’s Own Regenerative Chemistry

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### 4.1 *Beta-Carbolines as Endogenous Compounds*

Beta-carbolines are not foreign substances introduced from outside the body—they are endogenous molecules produced naturally in mammalian tissues. They have been identified in:

- ♦ Human plasma and platelets
- ♦ Rat whole brain, forebrain, arcuate nucleus, and adrenal glands
- ♦ The human pineal gland (6-methoxy-tetrahydro-beta-carboline has been identified as a major constituent)
- ♦ Human urine and cerebrospinal fluid

These compounds are synthesized endogenously from tryptophan and tryptophan-derived indoleamines through the Pictet-Spengler condensation reaction. This means the body possesses the enzymatic machinery to produce its own beta-carbolines.

### 4.2 *Developmental Changes in Endogenous Levels*

A 2021 study (*Frontiers in Aging Neuroscience*) specifically tracked beta-carboline alkaloid levels in newborn rats from birth through 29 days and in aging rats from 2 to 18 months. The key findings:

- ♦ Harmine is a naturally and widely distributed endogenous substance in different mammals and humans
- ♦ Exposure levels show high dependence on developmental and physiological state, including aging, gender, and race
- ♦ In addition to exogenous ingestion, spontaneous synthesis is likely an important source in mammals

This research directly supports the hypothesis that endogenous beta-carboline levels are highest during periods of rapid development and growth and decline with age—paralleling the decline in regenerative capacity that characterizes aging.

### *4.3 The Pineal Connection*

The pineal gland is of particular interest. 6-methoxy-tetrahydro-beta-carboline (pinoline) has been identified as a major constituent of the human pineal gland. Both pinoline and tetrahydro-beta-carboline possess specific binding sites in the pineal, adrenals, and specific areas of the brain.

The pineal gland's activity is regulated by light exposure—melatonin and related compounds are produced primarily in darkness. This creates a direct biochemical link between darkness, pineal activation, endogenous beta-carboline production, and regenerative signaling.

## 5. The Kaya Kalpa Dark Retreat Hypothesis

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### *5.1 Historical Context*

Kaya kalpa (Sanskrit: “body transformation”) is a practice documented in Ayurvedic and Siddha medical traditions involving extended periods of isolation in darkness, combined with specific herbal preparations and controlled nutrition. Historical accounts—including those attributed to Tapasviji Maharaj and descriptions in the Charaka Samhita—document remarkable regenerative outcomes including restoration of hair color, regrowth of teeth, restoration of youthful skin, and dramatic life extension.

Similar practices involving extended darkness are found in Tibetan Buddhist Dzogchen tradition (dark retreat / Yangti practice) and in Taoist cultivation practices. However, a significant distinction exists between these traditions in their reported outcomes. Dzogchen dark retreat is primarily oriented toward deepening awareness and is understood to be restorative—supporting the practitioner's contemplative stability and vitality—but the tradition does not typically claim or emphasize the degree of somatic regeneration described in the Kaya Kalpa accounts. The Kaya Kalpa, by contrast, is explicitly a regenerative technology, with historical descriptions of structural tissue renewal that go well beyond restoration.

This document proposes that this difference in outcome is not incidental but mechanistically explainable: the Kaya Kalpa tradition specifically combines darkness with herbal preparations, which the Yangti practice does not systematically include. If those preparations contained beta-carboline alkaloids—providing exogenous DYRK1A inhibition and MAO-A amplification of

pineal output—this would account for the difference. Darkness alone upregulates endogenous pineal beta-carboline production sufficiently to support the contemplative and restorative effects of Yangti. But reaching the threshold of deep somatic regeneration—progenitor cell reactivation across bone, cartilage, neural, and other tissues—may require the additional pharmacological drive that only exogenous beta-carboline administration provides.

It is also worth noting that kaya kalpa formulations were not uniform across traditions. The Ayurvedic and Siddha literature describes numerous distinct protocols, varying in herbal composition, duration, nutritional regime, and degree of sensory withdrawal. The formulations associated with the most dramatic regenerative outcomes—those describing structural tissue renewal—appear to represent a specialized and demanding subset of the broader practice, and the specific preparations involved are poorly documented in surviving texts. It is plausible that the most pharmacologically potent formulations have been lost, leaving only partial accounts of outcomes without the corresponding methodology.

## 5.2 *The Proposed Mechanism*

The dark retreat environment creates a unique biochemical context that may amplify the regenerative pathways activated by beta-carboline alkaloids. Critically, the relationship between exogenous harmala alkaloids and darkness is not merely additive—published research demonstrates a direct biochemical synergy that could create a positive feedback loop of regenerative signaling.

### 5.2.1 DIRECT BIOCHEMICAL SYNERGY WITH PINEAL OUTPUT IN DARKNESS

Sustained darkness maximally activates the pineal gland, upregulating melatonin synthesis via N-acetyltransferase (NAT) and increasing production of endogenous beta-carbolines (pinoline/6-methoxytetrahydro-beta-carboline is a major pineal constituent).

Exogenous harmala alkaloids are reversible MAO-A inhibitors, and published research demonstrates that they directly amplify the pineal gland's own output:

- ♦ Klein & Rowe (1969, *Molecular Pharmacology*) demonstrated in pineal organ culture that harmine inhibited serotonin oxidation while simultaneously stimulating melatonin production
- ♦ Klein & Weller (1970) further characterized this as an input-output regulatory system in the pineal gland
- ♦ King, Richardson & Reiter (1982, *Molecular and Cellular Endocrinology*) confirmed that harmine increased pineal NAT activity and pineal melatonin content in rats in vivo. Notably,

MAO inhibition during continuous light resulted in even greater NAT activity increases than during normal light-dark cycling

- ♦ A neuropharmacology review (Sandyk, 1990) confirmed that MAO inhibitors including harmine increase pineal concentrations of serotonin and N-acetylserotonin by enhancing N-acetyltransferase activity, and also increase melatonin, serotonin, and NAS in cerebrospinal fluid

The mechanism is straightforward: MAO-A inhibition by harmala alkaloids raises serotonin availability—the direct precursor for both melatonin and pineal beta-carbolines formed via Pictet-Spengler condensation. Consuming the seeds during darkness chemically amplifies the pineal’s own regenerative signaling. This is not merely additive—it could create a positive feedback loop where endogenous beta-carboline levels rise faster and higher than darkness alone would achieve.

#### 5.2.2 SHARED CHEMICAL CLASS AND OVERLAPPING REGENERATIVE PATHWAYS

Harmine, harmaline, and tetrahydroharmine are structurally analogous to endogenous pinoline and other pineal beta-carbolines. Both exogenous and endogenous compounds engage the same key regenerative targets documented throughout this paper: DYRK1A inhibition (progenitor cell reactivation), mitochondrial protection, neurogenesis, antioxidant effects, and growth-factor upregulation (BMP, BDNF, CCN2/CTGF).

Adding exogenous alkaloids during peak endogenous production layers independent pharmacological drive on top of the body’s own upregulated chemistry. This is structurally analogous to the synergy observed in ayahuasca (harmala + DMT), where beta-carbolines don’t merely protect DMT from degradation—they actively modulate serotonin/tryptamine metabolism and downstream neuroplasticity.

#### 5.2.3 ACCELERATION OF THE REGENERATIVE TIMELINE: THE PLANT THRESHOLD HYPOTHESIS

Dark-retreat effects on endogenous beta-carbolines and pineal output build gradually over days to weeks. A moderate exogenous dose of harmala alkaloids could provide an immediate “primer” boost to DYRK1A inhibition, mitochondrial function, and stem/progenitor cell signaling while the endogenous system ramps up. This could significantly accelerate the overall regenerative timeline of a dark retreat.

More fundamentally, this framework proposes that exogenous beta-carboline administration may not merely accelerate regeneration but may be necessary to cross the threshold at which deep somatic regeneration—structural tissue renewal—becomes possible at all. Endogenous beta-carboline production during darkness, while real and pharmacologically significant,

operates within the constraints of normal pineal biosynthesis. DYRK1A inhibition sufficient to reactivate quiescent progenitor cells across multiple tissue types may require alkaloid concentrations that the endogenous system alone cannot sustain. This would explain why Dzogchen dark retreat (Yangti), which does not systematically incorporate beta-carboline-containing plant preparations, produces restorative and contemplative effects but not the degree of structural tissue regeneration described in Kaya Kalpa accounts.

The hypothesis is thus specific: darkness provides the environmental substrate and initiates endogenous beta-carboline upregulation; exogenous harmala alkaloids provide the additional pharmacological concentration required to push DYRK1A inhibition into the range needed for progenitor cell reactivation at scale. Neither alone achieves what both together may accomplish. The Kaya Kalpa's insistence on herbal preparations as a non-negotiable component of the practice—not an optional adjunct—is consistent with this model.

The proposed approach during retreat—beginning with a moderate dose and adjusting based on subjective response—reflects the principle that the endogenous system is progressively contributing its own beta-carboline production as darkness deepens, and the combined load increases over time. The purpose is not to replace the endogenous process but to augment it. As the retreat deepens, subjective response rather than fixed dosing becomes the most reliable guide.

#### 5.2.4 RECAPITULATION OF EMBRYONIC BIOCHEMISTRY

The dark, enclosed environment of a dark retreat parallels the environment of the womb—sustained darkness, reduced sensory input, minimal metabolic demand. If endogenous beta-carboline levels are indeed highest during embryonic development (as the developmental research suggests), then a dark retreat may biochemically recapitulate aspects of the fetal environment, reactivating developmental pathways that have been dormant since birth.

#### 5.2.5 REDUCED METABOLIC DEMAND AND GROWTH HORMONE OPTIMIZATION

In a dark, restful state, the body's energy expenditure is minimized. Resources that would normally be allocated to activity, sensory processing, and stress response become available for repair and regeneration. Combined with controlled nutrition, this creates optimal conditions for the body to direct energy toward tissue renewal.

Growth hormone secretion peaks during deep sleep and is enhanced by darkness. Extended dark retreat with optimized sleep patterns could sustain elevated growth hormone levels, synergizing with beta-carboline-driven progenitor cell activation to enhance tissue regeneration. The convergence of reduced metabolic demand, growth hormone peaks, nutrient support, and

both endogenous and exogenous beta-carboline signaling creates what may be the optimal biochemical environment for systemic regeneration—affecting the full spectrum of tissues documented in this paper: neural, pancreatic, bone, and cartilage.

#### 5.2.6 ACCELERATION OF ENDOGENOUS AMṚTA: THE DIMENSION OF RECOGNITION

The regenerative mechanisms detailed above represent one dimension of what dark retreat may accomplish biochemically. In the contemplative traditions that practice extended darkness—particularly the Yangti of Dzogchen in Tibetan Buddhism and the Kaya Kalpa of Ayurvedic and Siddha medicine—somatic regeneration and the deepening of awareness are understood as simultaneous and inseparable expressions of a single process. The body's renewal and the clarification of awareness arise through the same chemistry.

These traditions describe the cultivation of an inner nectar—Amṛta in Sanskrit—through sustained darkness and sensory withdrawal. The function of this inner nectar is not primarily to generate perceptual phenomena but to support the direct, non-conceptual recognition of awareness itself—a clarity and openness that becomes increasingly accessible as the sensory field quiets and endogenous neurochemistry deepens. Within the framework of this document, Amṛta may correspond to the full spectrum of endogenous tryptamine and beta-carboline compounds produced by the pineal gland and brain under conditions of extended darkness: melatonin, pinoline (6-methoxy-tetrahydro-beta-carboline), related beta-tryptamines, and potentially N,N-dimethyltryptamine (DMT).

#### **Endogenous DMT—current evidence and theoretical significance:**

Dean et al. (2019, *Scientific Reports*) demonstrated that the enzyme required for DMT synthesis (INMT) is expressed in the cerebral cortex, pineal gland, and choroid plexus of both rats and humans. Extracellular DMT concentrations in the rat brain were found at levels comparable to canonical monoamine neurotransmitters such as serotonin and dopamine. DMT has also been detected in pineal gland perfusates of living rats (Barker et al., 2013). These findings establish that the mammalian brain possesses the enzymatic machinery to produce DMT endogenously.

DMT is rapidly degraded by MAO-A—the same enzyme that harmala alkaloids reversibly inhibit. Under normal conditions, any endogenous DMT produced would be metabolized almost immediately, preventing accumulation to functionally significant levels. MAO-A inhibition by exogenous harmala alkaloids would protect endogenous DMT from this rapid degradation, potentially allowing it to accumulate and engage its receptor targets—primarily 5-HT<sub>2A</sub> and sigma-1 receptors.

In the context of a dark retreat, this creates a layered amplification: sustained darkness upregulates pineal activity broadly, increasing production of melatonin, endogenous beta-carbolines, and potentially DMT. Exogenous harmala alkaloids then protect all of these endogenous compounds from MAO-mediated degradation while simultaneously contributing their own DYRK1A inhibition, mitochondrial protection, and progenitor cell reactivation. The result would be a progressive accumulation of endogenous regenerative and recognition-supporting neurochemistry that neither darkness alone nor the alkaloids alone could achieve.

A direct implication of this mechanism is a significant compression of the retreat timeline. In darkness alone, any endogenous DMT produced is degraded by MAO-A almost instantaneously under normal enzymatic conditions, preventing accumulation to functionally significant levels. The endogenous beta-carboline and melatonin buildup that darkness drives is real but gradual—traditional accounts and contemporary practitioners describe the deeper states of Yangti arising over days to weeks of continuous darkness. The administration of harmala alkaloids changes this fundamentally: MAO-A inhibition is present from the first dose, protecting endogenous tryptamines and beta-carbolines from degradation from the outset rather than waiting for endogenous production alone to reach threshold. The pharmacological conditions that darkness alone might require weeks to approximate are established biochemically within hours of the first dose. The depth of contemplative and neurochemical engagement that a practitioner might reach in the second or third week of an unaided dark retreat could, on this model, be accessible within the first days of a retreat combining darkness with harmala alkaloids.

The framework presented here does not depend solely on endogenous DMT—the confirmed endogenous beta-carbolines (pinoline and related compounds) already provide a robust mechanism for the effects attributed to dark retreat. If endogenous DMT production proves significant, it would represent an additional and potent layer within this system.

### *5.3 The Convergence of Traditional Knowledge and Modern Pharmacology*

The kaya kalpa texts describe administering specific herbal preparations during the dark retreat. If *Peganum harmala* (or a closely related beta-carboline-containing plant) was among those preparations—as proposed in this framework—then the traditional practice was empirically combining:

1. Environmental optimization for endogenous beta-carboline production (darkness)
2. Exogenous beta-carboline supplementation (herbal preparations)
3. Metabolic conditions favoring regeneration (rest, controlled nutrition, reduced demands)
4. Extended duration to allow cumulative regenerative effects

Modern pharmacology has independently identified these same mechanisms—DYRK1A inhibition, mitochondrial biogenesis, stem cell reactivation, neurogenesis—without knowing that a traditional practice may have been systematically exploiting them for centuries.

## 6. Proposed Daily Low-Dose Protocol

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Based on the pharmacological evidence, the following protocol is proposed for daily regenerative use of whole powdered *Peganum harmala* seed outside of a dark retreat context.

### 6.1 Dosage

Optimal regenerative dosing has not yet been established in human studies and is expected to vary meaningfully between individuals based on body weight, baseline MAO-A activity, metabolic rate, and sensitivity to inverse tolerance accumulation. The bell-shaped dose-response curve established in in vitro studies tells us that an optimum exists—but the peak of that curve cannot currently be mapped onto a specific oral dose of whole powdered seed. The motor impairment threshold (tremor, ataxia) that appears at higher doses is a serotonergic and cerebellar phenomenon operating through MAO-A inhibition—a distinct mechanism from the DYRK1A inhibition and mitochondrial pathways responsible for regenerative effects. These two sets of effects may have different dose-response curves entirely, and the appearance of motor effects does not necessarily signal that the regenerative optimum has been exceeded.

**Regenerative range:** The practical starting point is a dose sufficient to confirm pharmacological activity—indicated by mild cognitive or perceptual engagement, confirming blood-brain barrier penetration and receptor engagement. The upper bound is less clear. Some individuals may find their optimal range at low doses; others may find that higher doses, including those approaching or at the full MAO threshold of approximately 3g, feel more consistent with robust physiological engagement. Individual response and subjective experience are the most honest guides available given the current state of the evidence. The goal is not the lowest possible dose but the dose at which perceptible engagement is present without uncomfortable serotonergic loading.

**Motor and serotonergic threshold (moderate dose):** Tremor, ataxia, and serotonergic restlessness begin to appear as doses increase. For whole powdered seed, significant motor effects in humans typically begin in the range of approximately 3 grams (delivering roughly 90–150mg total alkaloids at the 3–5% content range established in Section 2), representing the practical upper limit of safe daily use. This threshold varies with individual sensitivity and is lowered by the inverse tolerance accumulation of daily dosing.

**Chronic safety ceiling:** A three-month chronic toxicity study in rats found no adverse effects at doses of 2.5–10mg/kg/day of pure harmine—for an 80kg person, roughly 200–800mg of pure harmine daily, substantially above what a low-dose whole-seed protocol delivers. This establishes that the regenerative dose range operates with a substantial margin below the chronic toxicity threshold.

**The full MAO inhibition dose—well within the safety range:** A dose of approximately 3–5 grams of whole powdered seed produces full reversible MAO-A inhibition and may be associated with motor effects—tremor, mild ataxia—that represent the practical upper limit for regular daily use. Importantly, this motor threshold is a pharmacological side effect, not a toxicity marker—it sits well within the chronic safety range.

**Protective effects across organ systems within the therapeutic range:** A critical and often underappreciated feature of beta-carboline alkaloids is that at therapeutic doses they are not merely non-toxic but actively protective across multiple organ systems simultaneously. The same compounds that burden these systems at excessive doses defend them at low and moderate doses—a classical hormesis pattern that runs consistently through the published literature.

**Neuroprotection:** A systematic review of preclinical studies (PubMed, 2016) found harmine administration associated with reduced excitotoxicity, attenuation of neuroinflammation and oxidative stress, and increased BDNF levels in hippocampal neurons, with improvement in memory and learning across multiple animal models. These effects operate through MAO inhibition, acetylcholinesterase inhibition, upregulation of glutamate transporters, and direct ROS scavenging. Consistent with this profile, harmine was commercially sold by Merck beginning in the 1920s as a remedy for Parkinson’s disease and parkinsonian tremor—an early pharmaceutical recognition of its neuroprotective properties predating modern mechanistic understanding (Djamshidian et al., 2016). Antihypoxic activity—protection of neural tissue against oxygen deprivation—has also been confirmed in animal models (Goldaeva et al., 2021, *Open Access Macedonian Journal of Medical Sciences*).

**Mitochondrial protection:** Documented in detail in Section 3.3. Kim et al. (2001, *Journal of Neurochemistry*) demonstrated protection of brain mitochondria against oxidative damage across all three major alkaloids; Réus et al. (2012) confirmed increased mitochondrial complex I and IV activity. The dose-dependent biphasic profile here is the clearest expression of the hormesis pattern: protective at low-moderate doses, inhibitory at high concentrations.

**Hepatoprotection:** Beta-carboline alkaloids protect against chemically induced liver damage, reduce hepatic oxidative stress markers, and preserve liver enzyme profiles under toxic challenge. A recent review evaluated beta-carbolines specifically for hepatoprotective and anticancer potential in the context of hepatocellular carcinoma, identifying multi-targeted protective mechanisms (beta-carboline/HCC review, ResearchGate, 2024). The 28-day subchronic study found no liver pathology at 15 and 45 mg/kg/day total alkaloid extract, with adverse changes appearing only at 150 mg/kg/day and reversing fully after drug withdrawal (ScienceDirect, 2019).

**Renoprotection:** Nephroprotective effects have been documented alongside hepatoprotective properties in pharmacological reviews of *P. harmala* (Moloudizargari et al., 2013, PMC). Renal markers—creatinine and urea—remained stable at therapeutic dose levels in subchronic toxicity studies.

**Cardioprotection:** Harmine effectively treats cardiac hypertrophy in spontaneously hypertensive rat models, operating through the DYRK1A pathway—the same mechanism underlying its regenerative effects across other tissues (PMC, 2022). Vasorelaxant effects of harmine and harmaline on vascular smooth muscle have been demonstrated (Berrougui et al., 2006, *Pharmacological Research*), and calcium channel modulation by harmala alkaloids in vascular and intestinal smooth muscle has been confirmed (Karaki et al., 1986, *British Journal of Pharmacology*). All three major alkaloids have also been shown to increase myocardial contractile force in anesthetized dogs (Aarons et al., 1977, *Journal of Pharmaceutical Sciences*).

**Anti-inflammatory and antioxidant:** Documented throughout the literature and elaborated in Section 3.4. These systemic effects contribute to the protective profile across all organ systems listed above—the anti-inflammatory and ROS-scavenging properties are not isolated to a single tissue but operative wherever the alkaloids distribute, which includes brain, liver, kidney, heart, and skeletal tissue.

Taken together, the therapeutic-dose profile of whole powdered *Peganum harmala* seed is one of simultaneous active protection across the body's major organ systems—the same systems that would eventually be burdened by excessive doses. This systemic protective pattern is consistent with the traditional use of this plant as a broad-spectrum medicinal across cultures spanning millennia, and provides a pharmacological basis for understanding why low-dose chronic use produces benefit rather than harm.

**Chronic safety data:** A 28-day subchronic toxicity study using total alkaloid extract of *P. harmala* seeds in rats established a no-observed-adverse-effect level (NOAEL) of 45 mg/kg/day of total alkaloid extract. Scaling to an 80kg person, this corresponds to 3,600mg of total alkaloids daily. At the typical seed alkaloid content of 3–5%, this equates to approximately 72–120 grams of whole seed per day—roughly fifteen to forty times the full MAO-inhibiting dose of 3–5g, and orders of magnitude above any proposed regenerative protocol.

**Acute toxicity in context:** The best available human clinical reference point is a documented case in which a 45-year-old woman ingested approximately 50 grams of *P. harmala* seeds—a dose roughly seventeen times the full MAO threshold. She experienced nausea, vomiting, dizziness, tremor, ataxia, and confusion with mild hypotension, but was discharged in good condition within 18 hours with no lasting harm. This single case illustrates both that acute toxicity does occur at extreme doses and that even those doses are not acutely lethal in a healthy adult.

Animal LD50 data for isolated alkaloids by oral administration: harmaline approximately 119 mg/kg and harmine approximately 250 mg/kg in mice. Allometric scaling to humans and the oral route substantially increases these figures, and the whole-seed matrix further buffers absorption compared to isolated alkaloids.

**Practical summary for an 80kg person:**

- ◆ Regenerative target range: unknown precisely; individual titration based on subjective response, from minimal pharmacological engagement up to and potentially including the full MAO threshold
- ◆ Full MAO inhibition threshold: approximately 3–5g seed (~90–250mg total alkaloids at 3–5% alkaloid content)—motor side effects possible but not a toxicity marker, and not necessarily the ceiling of regenerative benefit
- ◆ Chronic NOAEL equivalent: approximately 72–120g seed per day (based on 45mg/kg/day total alkaloid extract scaled to 80kg, at 3–5% alkaloid content)—a large multiple of any proposed protocol
- ◆ Documented severe acute overdose: 50g—significant symptoms, full recovery within 18 hours
- ◆ True lethal dose: unknown but substantially above any of the above thresholds

As with any biologically active compound, toxicity exists at sufficient dose. But the distance between the therapeutic range and any genuinely dangerous dose is large, and the compounds are actively protective to the organs they would eventually burden at excess. Potency—the fact

that small amounts produce meaningful pharmacological effects—is not a liability but a feature: it means the therapeutic range requires minimal seed consumption, and the margin between effect and toxicity is wide.

### 6.2 *Inverse Tolerance Consideration*

Beta-carboline alkaloids demonstrate inverse tolerance through cumulative reversible MAO-A inhibition. With daily dosing, the active MAO-A enzyme pool gradually decreases because new enzyme is inhibited before the previous dose's effect has fully cleared. This means:

- ◆ Effects may strengthen over the first 5–7 days of daily use at a constant dose
- ◆ Beginning at the lower end of one's individual range and observing the response over a week before adjusting is advisable
- ◆ If motor effects or excessive serotonergic effects appear after several days, reduce dose rather than increase—the inverse tolerance effect means the same dose is delivering progressively greater pharmacological impact

### 6.3 *Timing Rationale*

**Morning dose:** Covers the cortisol peak when oxidative stress and inflammatory signaling are highest. Provides mitochondrial protection during the period of maximum metabolic demand. Supports glucose metabolism through the DYRK1A/beta-cell pathway during the post-fasting morning window.

**Evening dose:** Aligns with the body's nocturnal regenerative window when growth hormone secretion peaks during deep sleep. Supplements the pineal gland's own nighttime beta-carboline production. Supports the repair and regeneration processes that occur preferentially during sleep.

### 6.4 *Supporting Factors*

The alkaloid protocol would be optimized by:

- ◆ Whole-food, nutrient-dense nutrition providing the raw materials for tissue regeneration
- ◆ Regular exercise to independently stimulate PGC-1 $\alpha$  and mitochondrial biogenesis, synergizing with the alkaloids' mitochondrial effects
- ◆ Clean environmental air and water to minimize toxic burden on the body's repair systems
- ◆ Adequate sleep in darkness to support endogenous pineal beta-carboline and growth hormone production

- ◆ Key supplements: NAC (glutathione precursor), vitamin B12, vitamin D3, magnesium, and selenium to support the detoxification and regenerative pathways

## 7. Dark Retreat Protocol Considerations

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Within a formal dark retreat context, the biochemical framework developed in this document points toward specific practical considerations that differ meaningfully from a standard daily-use protocol. The interaction between sustained darkness, endogenous pineal activation, and exogenous harmala alkaloids is dynamic and progressive—not static—requiring an adaptive approach across the duration of the retreat.

### *7.1 Duration*

Traditional kaya kalpa retreats are documented at durations ranging from weeks to months. The biochemical rationale supports this extended timescale: cumulative effects on endogenous beta-carboline production, progenitor cell reactivation, and neural regeneration would increase progressively with duration. The pineal gland's output does not switch on immediately but increases over days as the absence of light stimuli is sustained. Similarly, DYRK1A-dependent progenitor cell reactivation and the downstream processes of differentiation and tissue integration proceed on biological timescales of weeks, not hours.

A minimum effective duration for significant regenerative effects is unknown but is likely measured in weeks rather than days. Short retreats of three to five days may produce meaningful neurochemical shifts without reaching the deeper tissue-regenerative thresholds that longer retreats appear to target.

However, the combination of darkness with harmala alkaloids is expected to compress this timeline significantly—and this compression is a direct, mechanistically grounded inference rather than speculation. In darkness alone, the process of endogenous neurochemical deepening is limited by the rate at which the pineal gland and related systems can ramp up production of beta-carbolines and related compounds, and by the fact that any endogenous DMT produced is immediately degraded by uninhibited MAO-A. Progress is real but gradual. With harmala alkaloids present, MAO-A inhibition is established from the first dose—protecting endogenous tryptamines and amplifying pineal output from the outset. The pharmacological conditions that darkness alone builds toward over weeks are present biochemically from early in the retreat.

The practical implication is that the combination protocol may achieve within the first days what an unaided dark retreat might require weeks to approach, particularly for the dimension of contemplative deepening and recognition described in section 5.2.6. This does not eliminate the value of duration—the regenerative processes of tissue differentiation and integration still require biological time—but it suggests that the effective retreat length needed to reach threshold depth of experience may be substantially shorter than traditional darkness-only practice requires. This has meaningful implications for the accessibility and design of modern dark retreat protocols.

## 7.2 Dosing

The dosing relationship during dark retreat is not fixed but should be understood as a conversation between endogenous and exogenous supply over time.

**Entry phase (days 1–5):** Endogenous pineal beta-carboline production has not yet fully upregulated. A low regenerative dose of whole powdered seed can be used to provide immediate DYRK1A inhibition and mitochondrial priming while the endogenous system activates.

**Deepening phase (days 5 onward):** As sustained darkness progressively amplifies pineal output, the combined endogenous and exogenous load increases. The inverse tolerance effect compounds this dynamic: accumulated MAO-A inhibition means each dose has progressively greater pharmacological impact. Monitoring subjective response—particularly serotonergic loading signals such as restlessness, sleep disruption, or motor effects—becomes the primary guide for dose adjustment in this phase.

**Signals to reduce dose:** Tremor, ataxia, or motor unsteadiness are clear signals of excessive serotonergic load. Subtler signals include sleep disruption, vivid but agitated rather than luminous dream states, or heightened anxiety. These indicate the protocol has overshot the therapeutic window.

**Signals the protocol is working:** Deepening sleep quality, increased dream luminosity and clarity, heightened sensory sensitivity during waking periods, warmth and vitality in the extremities, increased urinary frequency (a traditional marker of increased kidney filtration and tissue turnover).

### 7.3 Nutrition

Nutrition during dark retreat serves a different function than ordinary sustenance—it is directed specifically toward providing the raw materials for active tissue regeneration rather than simply maintaining homeostasis.

Priorities include: adequate tryptophan—the direct biosynthetic precursor to serotonin, melatonin, pinoline, and potentially DMT, all produced via the same indoleamine pathway that darkness and MAO-A inhibition are collectively upregulating. With the entire pineal-tryptamine axis amplified, ensuring abundant tryptophan availability from dietary sources becomes nutritionally significant in a way it would not be under ordinary conditions. High-tryptophan foods include animal proteins (eggs, dairy, poultry, fish), seeds (pumpkin, sesame, sunflower), legumes, and nuts. Complete amino acid availability more broadly (essential for progenitor cell differentiation and protein synthesis in newly formed tissue); essential fatty acids, particularly DHA, for neural membrane reconstruction during neurogenesis; minerals required for osteogenesis and chondrogenesis (calcium, magnesium, phosphorus, silica); and adequate B-vitamins, including B12, for methylation reactions underlying both DNA synthesis in proliferating cells and neurotransmitter metabolism. The kaya kalpa tradition's emphasis on specific foods during retreat—traditionally including milk, ghee, honey, and specific herbs—may reflect empirical optimization of these nutritional requirements accumulated over centuries of practice.

Caloric restriction to a moderate degree (not fasting, but eating less than full demand) may support the growth hormone optimization discussed in section 5.2.5 and has independent evidence for promoting autophagy and cellular renewal.

### 7.4 Monitoring

In the absence of laboratory testing during retreat, subjective and observable markers provide the primary feedback channel:

**Regenerative indicators:** Increased warmth and circulation in extremities; changes in nail and hair growth rate; enhanced skin texture or tone; subjective sense of tissue vitality and density; deepening sleep architecture and more luminous or stable dream states.

**Cognitive and contemplative indicators:** Increasing stability and clarity of awareness during both waking and hypnagogic states; spontaneous arising of visual phenomena during darkness (phosphenes, geometric forms, light phenomena) consistent with the Yangti accounts of inner luminosity arising; and progressive stabilization of non-conceptual recognition.

**Excess-load indicators:** Any of the motor, anxious, or agitated states noted above under dosing; excessive serotonergic restlessness; or paradoxical sleep disruption despite physical stillness.

Journaling in darkness (or recording voice notes) provides a longitudinal record that can be reviewed after the retreat to correlate protocol variables with subjective experience.

## 8. Research Gaps and Future Directions

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The following areas require further investigation:

1. Extended tissue mapping of DYRK1A inhibition effects across additional stem and progenitor cell populations—particularly dental, follicular, hepatic, and renal progenitors—building on the established evidence in pancreatic, neural, bone, and cartilage tissues
2. Human longitudinal studies measuring biomarkers of aging (telomere length, epigenetic clocks, mitochondrial function) during extended low-dose beta-carboline protocols
3. Direct measurement of endogenous beta-carboline levels during extended dark retreat in humans—no published study has tracked pinoline, 6-methoxy-TH $\beta$ C, or related compounds longitudinally across a multi-week dark retreat
4. Endogenous DMT status during darkness and MAO inhibition—the question of whether significant endogenous DMT is produced under conditions of sustained darkness, and whether MAO-A inhibition allows accumulation to receptor-engaging levels, remains unresolved and represents one of the most consequential open questions in this framework
5. Harmala alkaloids and dark retreat in combination—no controlled study has examined the biochemical or clinical effects of beta-carboline supplementation specifically within extended dark retreat conditions; this combination is the central hypothesis of this document and represents the most direct research target
6. Systematic mapping of organ-protective dose ranges—hepatoprotective and nephroprotective effects have been documented but not comprehensively characterized across tissues or across the full dose-response curve in humans
7. Dose-response optimization for regenerative effects specifically, separate from MAO inhibition and psychoactive effects
8. Interaction mapping between exogenous beta-carbolines and endogenous pineal production during darkness
9. Characterization of harmine’s unidentified “Target 2”—the PKA-activating mechanism responsible for pro-differentiation effects that remains unexplained in mechanistic terms

10. Comparative analysis of kaya kalpa herbal preparations across Ayurvedic, Siddha, and related traditions to identify beta-carboline-containing plants in traditional formulations, and to assess whether beta-carboline sourcing was a deliberate or empirically discovered feature of those protocols

## 9. Conclusion

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The published pharmacological evidence establishes that *Peganum harmala* beta-carboline alkaloids simultaneously engage multiple pathways directly implicated in aging and regeneration: DYRK1A inhibition reactivating quiescent progenitor cells, mitochondrial protection and enhancement, neurogenesis, osteogenesis and chondrogenesis, inhibition of tissue-degrading processes (osteoclast suppression, cartilage protection), antioxidant and anti-inflammatory activity, and upregulation of growth factors including BMPs and BDNF. These compounds are endogenous to the human body, with levels that appear to correlate with developmental stage and decline with age.

The breadth of regenerative effects is remarkable: a single natural compound complex has been demonstrated to drive regeneration across neural tissue, pancreatic tissue, bone, and cartilage—while simultaneously protecting these tissues from degradation. No synthetic pharmaceutical currently in development matches this scope of multi-tissue regenerative activity.

The kaya kalpa dark retreat tradition may represent an empirically developed protocol that combines environmental optimization of endogenous beta-carboline production with exogenous supplementation and metabolic conditions favoring regeneration. Modern pharmacology is independently converging on the same mechanisms—DYRK1A inhibition, mitochondrial biogenesis, stem cell reactivation, neurogenesis—that this traditional practice appears to have exploited for centuries.

But the framework developed here points beyond regeneration in the strictly somatic sense. The evidence for endogenous beta-carboline and potentially DMT production during sustained darkness, and the pharmacological correspondence between exogenous beta-carboline/tryptamine combinations and the endogenous neurochemistry of dark retreat, suggests that the kaya kalpa and Yangti traditions were cultivating something that modern pharmacology is only beginning to articulate: a systematic technology for the accumulation of endogenous Amṛta—the inner nectar of melatonin, pinoline, and tryptamine compounds—that simultaneously renews the body and supports direct recognition of awareness itself.

In this understanding, the regenerative and the contemplative are not separate aims but two expressions of a single biochemical process. The darkness rebuilds the body and illuminates awareness through the same chemistry. Harmala alkaloids, taken in low regenerative doses during extended dark retreat, bridge the exogenous and endogenous dimensions of this process—priming the system at entry and gradually augmenting the practitioner’s own emerging biochemistry as the retreat deepens.

## References

This summary was compiled from published peer-reviewed research and theoretical analysis. It is intended for researchers and does not constitute medical advice. Key references include: Wang et al. (2015) *Nature Medicine*; Yonezawa et al. (2011) *Biochemical and Biophysical Research Communications* (bone); Shohayeb et al. (2012) PubMed—chondrogenic and chondroprotective effects; Klein & Rowe (1969) *Molecular Pharmacology* (harmine-pineal melatonin); Klein & Weller (1970) *In Vitro* (pineal input-output regulation); King, Richardson & Reiter (1982) *Molecular and Cellular Endocrinology* (harmine-NAT activity); Kim et al. (2001) *Journal of Neurochemistry* (mitochondrial protection); Réus et al. (2012) *Depression Research and Treatment* (mitochondrial complex activity); Li et al. (2021) *Frontiers in Aging Neuroscience*; Morales-García et al. (*Scientific Reports*, neurogenesis); Dirice et al. (2016) *Diabetes*; Nakagawa et al. (2010) *Chemico-Biological Interactions*; *Nature Bone Research* (2023)—small-molecule amines in bone homeostasis; Dean et al. (2019) *Scientific Reports*—endogenous DMT and INMT expression in mammalian brain; Barker et al. (2013)—DMT in rat pineal perfusates; Asgarpanah & Ramezanloo (2012)—comprehensive review of *P. harmala* alkaloid content (2–5% total); Chinese Academy of Sciences HPLC study (PMC, 2018)—harmine 2.02%, harmaline 2.87% in seeds; Euro-Mediterranean Journal HPLC study (2024)—harmine 2.11%, harmaline 2.38%; Leishmania PMC study—harmine 1.7%, harmaline 3.0%; Systematic review of harmine neuroprotection in hippocampus (PubMed, 2016); Djamshidian et al. (2016) *Movement Disorders*—historical Parkinson’s use; Goldaeva et al. (2021) *Open Access Macedonian Journal of Medical Sciences*—antihypoxic activity; Harmine and cardiac hypertrophy via DYRK1A (PMC, 2022); Berrougui et al. (2006) *Pharmacological Research*—vasorelaxant effects; Karaki et al. (1986) *British Journal of Pharmacology*—calcium channel modulation; Aarons et al. (1977) *Journal of Pharmaceutical Sciences*—cardiovascular actions; Moloudizargari et al. (2013) PMC—hepatoprotective and nephroprotective review; Zhang et al. (2016)—oral LD50 of harmaline and harmine in mice; 28-day subchronic NOAEL study (ScienceDirect, 2019); 50g acute overdose case report (PMC, 2014).

