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Review Article

Stilbenoid Scaffolds at the Interface of Anxiety and Glucose Homeostasis: A Mechanistic and Translational Review of Preclinical Evidence and Evaluation Strategies

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ABSTRACT

Anxiety and type 2 diabetes mellitus (T2DM) are frequently associated conditions that share several pathophysiological mechanisms, including oxidative stress, neuroinflammation, insulin resistance, and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. The bidirectional relationship between metabolic dysfunction and anxiety highlights the need to investigate pharmacological agents that may influence both neurological and metabolic parameters. Lunularin, a dihydrostilbene and gut microbial metabolite of resveratrol, has attracted interest because of its potential biological activities. However, its anxiolytic potential and influence on glucose homeostasis remain insufficiently investigated. The present study aims to investigate the anxiolytic potential of lunularin and its influence on glucose homeostasis in an experimental model of type 2 diabetes mellitus. Diabetes will be induced in Wistar rats using streptozotocin and nicotinamide (STZ–NA). Animals will be divided into appropriate experimental groups, including normal control, diabetic control, standard treatment, and lunularin-treated groups at selected dose levels. The anxiolytic potential of lunularin will be evaluated using behavioural paradigms such as the elevated plus maze and actophotometer, while locomotor activity and motor coordination will be assessed to distinguish anxiolytic effects from nonspecific behavioural changes. Glucose homeostasis will be evaluated through fasting blood glucose, glycated haemoglobin, and relevant metabolic parameters. Biochemical investigations may include oxidative stress markers, antioxidant status, and selected molecular pathways associated with metabolic and behavioural regulation.

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Histopathological examination of relevant tissues will provide additional evidence of treatment-associated changes.The study is expected to provide preliminary experimental evidence regarding the relationship between lunularin-mediated behavioural responses and glucose regulation in diabetic animals. The findings may contribute to understanding the pharmacological potential of lunularin and identify directions for further mechanistic and translational research.

INTRODUCTION

Anxiety disorders are the most prevalent group of mental disorders. They are characterised by excessive fear, worry and avoidance behaviour that persist beyond the triggering situation and interfere with work, relationships and health [1,2]. Depending on the survey methodology and the population studied, lifetime prevalence estimates run from roughly 15% to more than 30%, and the burden is carried disproportionately by people who also live with a chronic physical illness [1,2]. Generalised anxiety disorder, panic disorder, social anxiety disorder and specific phobias differ in presentation, yet they share overlapping circuitry involving the amygdala, prefrontal cortex and hippocampus, and a shared dependence on GABAergic, serotonergic and noradrenergic signalling [1,3].

Diabetes mellitus is a chronic metabolic disorder defined by persistent hyperglycaemia resulting from defective insulin secretion, defective insulin action or both [5]. The International Diabetes Federation estimated that 537 million adults aged 20–79 years were living with diabetes in 2021, with a projected rise to 783 million by 2045, and type 2 diabetes accounts for the large majority of these cases, over 90% by most estimates [4,5]. T2DM is not only a disease of the pancreas, liver and muscle. It is also a disease of the brain: sustained hyperglycaemia, insulin resistance and the oxidative and inflammatory milieu that accompany them alter neuronal function, synaptic plasticity and mood regulation [27,28].

The clinical consequence is a well-documented comorbidity. Systematic reviews and meta-analyses report that around 14–15% of adults with diabetes meet criteria for an anxiety disorder, and that as many as 40% report clinically elevated anxiety symptoms, a burden clearly greater than in people without diabetes [6,7]. Anxiety in a person with diabetes is not merely an emotional overlay. It is associated with poorer self-management, more glycaemic variability, more hypoglycaemia-related fear and worse outcomes [6,7]. The relationship is bidirectional: chronic anxiety activates stress hormone pathways that raise glucose and worsen insulin resistance, while diabetes and its complications provide ongoing physiological stressors that sustain anxiety [8,27].

Current pharmacotherapy handles the two problems separately. Benzodiazepines act quickly, but sedation, psychomotor impairment, tolerance and dependence restrict their use to short courses [9,10]. Selective serotonin reuptake inhibitors and related antidepressants are first-line for long-term treatment, yet they take weeks to act and some are associated with weight gain and altered glycaemic control [9]. Antidiabetic agents, in turn, are not designed to modify the neurobehavioural complications of diabetes. A single agent with credible activity in both domains would be of obvious value, and natural products are a logical place to look [11].

Stilbenoids are plant-derived polyphenols built on a C6 –C2–C6 skeleton. Resveratrol, the archetype of the class, has been studied for more than two decades for its antioxidant, anti-inflammatory, neuroprotective and metabolic effects [12,13]. Its clinical promise has been limited by poor oral bioavailability and extensive first-pass metabolism, which has pushed attention toward more stable analogues, such as pterostilbene, and toward the metabolites themselves, some of which may be active in their own right [14,15]. Lunularin is one such molecule. It is a dihydrostilbene (bibenzyl) that occurs naturally in liverworts, has been reported in several medicinal orchids, and is produced in significant amounts by human gut bacteria from dietary resveratrol [16–18]. Despite this, the pharmacology of lunularin in the central nervous system and in glucose metabolism is almost entirely unexplored.

1.1 Rationale for this review

Three observations motivate a focused review of lunularin. First, anxiety and impaired glucose homeostasis share upstream mechanisms (oxidative stress, neuroinflammation, HPA-axis hyperactivity and

impaired insulin signalling) that are plausible targets for polyphenols. Second, saturated bibenzyl structures like lunularin are chemically different from resveratrol in ways that could change stability, lipophilicity and tissue distribution. Third, there is no published systematic evaluation of lunularin across graded doses in a validated model of T2DM with neurobehavioural readouts. A structured account of what is known, what can reasonably be inferred and what must be tested is therefore timely.

1.2 Aim and objectives of the review

The aim of this review is to evaluate the evidence and mechanistic rationale for lunularin as a dual-acting anxiolytic and glucose-regulating candidate. The specific objectives are:

- to summarise the neurobiology of anxiety and the pathophysiology of T2DM, with emphasis on shared mechanisms;
- to describe the chemistry, sources, biosynthesis and metabolic origin of lunularin and place it within the stilbenoid family;
- to critically analyse the anxiolytic and antidiabetic evidence for stilbenoids, separating direct evidence for lunularin from inference;
- to outline an experimental framework based on the STZ–NA rat model and established behavioural tests, including dose selection and controls;
- to discuss pharmacokinetic, safety and translational challenges and to identify priorities for future work.

2. Scope and Approach

This is a narrative review rather than a systematic review or meta-analysis. The literature was organised around five questions: what drives anxiety, what drives T2DM, where the two converge, what is known about stilbenoids in those pathways, and what is specifically known about lunularin. Primary studies, systematic reviews and meta-analyses from pharmacology, neuroscience, endocrinology and natural-product chemistry were considered, with priority given to peer-reviewed work in recognised journals and to methodological papers that define the behavioural and disease models discussed.

Two cautions apply throughout. The first is that direct experimental evidence on lunularin is sparse. Where this review draws conclusions about lunularin from resveratrol, pterostilbene or dihydroresveratrol, this is stated explicitly, and such statements should be read as hypotheses and not as findings. The second is that most mechanistic evidence for stilbenoids comes from cell culture and rodent studies, and results from human trials, particularly of resveratrol, have been mixed. Evidence is graded in this review as *direct* (studied for lunularin itself), *class-based* (studied for stilbenoids or bibenzyls) or *inferred* (a mechanistic extrapolation).

Table 1: Evidence Grading Used in This Review

Grade	Definition	Example	Confidence
Direct	Experimental data on lunularin itself	Chemical identity; occurrence in liverworts; formation by gut microbiota [16–18]	Moderate for chemistry; low for pharmacology
Class-based	Data on resveratrol, pterostilbene or other stilbenoids	AMPK/SIRT1 activation; antidepressant-like effects in rodents [19–22]	Moderate in rodents; mixed in humans
Inferred	Mechanistic extrapolation to lunularin	Possible GABAergic or antioxidant anxiolysis	Low; hypothesis only

3. Anxiety Disorders: Burden, Neurobiology and Current Therapy

3.1 Epidemiology and clinical burden

Anxiety disorders typically begin in childhood, adolescence or early adulthood, follow a chronic and relapsing course and are associated with substantial disability, reduced quality of life and increased healthcare use [1,2]. They are also strongly associated with cardiometabolic disease, and the association is not explained by lifestyle alone [8]. In India and other low- and middle-income settings, under-recognition and limited access to treatment mean that anxiety in people with chronic disease frequently goes untreated, which makes safe, affordable and disease-compatible options especially valuable [2].

3.2 Neurobiological basis

Anxiety arises from dysregulation of threat-processing circuits. The amygdala assigns emotional significance to stimuli and drives fear responses, the prefrontal cortex exerts top-down regulation, and the hippocampus provides contextual information and also governs negative feedback on the HPA axis [1,3]. In anxiety states the amygdala is hyper-responsive and prefrontal inhibitory control is weakened, which results in exaggerated reactions to ambiguous or minor threats.

GABAergic signalling. GABA is the main inhibitory neurotransmitter in the brain, and GABA-A receptors in the amygdala, hippocampus and cortex tune the excitability of anxiety circuits. Benzodiazepines such as diazepam bind an allosteric site on the GABA-A receptor and increase the frequency of chloride channel opening, which explains both their rapid anxiolytic action and their sedative, ataxic and amnestic side effects [10,23]. Reduced GABAergic tone has been consistently reported in anxiety disorders, so any candidate with GABA-A modulatory activity is of interest, provided it separates anxiolysis from sedation.

Monoaminergic signalling. Serotonin and noradrenaline modulate amygdala and prefrontal activity. Serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors remain first-line long-term treatments, and several polyphenols, including resveratrol, increase central monoamine levels in rodents, in part through monoamine oxidase inhibition [9,19].

HPA axis and glucocorticoids. Stress activates corticotropin-releasing hormone neurons in the paraventricular nucleus, driving ACTH release and adrenal glucocorticoid secretion. Under normal conditions, glucocorticoids feed back via hippocampal and hypothalamic receptors to end the response. Chronic stress and chronic anxiety blunt this feedback, and sustained hypercortisolaemia damages hippocampal neurons, reduces BDNF and promotes visceral adiposity and insulin resistance [8]. This is a pivotal point of intersection with metabolism and is discussed in Section 5.

Oxidative stress and neuroinflammation. The brain consumes about a fifth of resting oxygen, is rich in oxidisable lipids and has relatively modest antioxidant defences. Elevated markers of lipid peroxidation, reduced superoxide dismutase, catalase and glutathione activity, and raised pro-inflammatory cytokines have been reported in anxiety and mood disorders [24,25]. Activated microglia release interleukin-1β, interleukin-6 and tumour necrosis factor-α, which impair synaptic plasticity and sensitise threat circuits [26]. Because polyphenols such as stilbenoids both scavenge reactive species and modulate inflammatory signalling, this is the mechanistic domain in which their relevance to anxiety is most easily argued.

3.3 Current pharmacotherapy and its limits in diabetes

Treatment guidelines recommend cognitive behavioural therapy together with pharmacotherapy, most commonly SSRIs or SNRIs, with pregabalin, buspirone and short-term benzodiazepines as alternatives [9]. In patients with diabetes these options face additional constraints, summarised in Table 2.

Table 2: Principal Anxiolytic Classes and Limitations Relevant to Patients with Diabetes

Class	Main mechanism	Strengths	Limitations relevant to diabetes
Benzodiazepines (e.g. diazepam)	Positive allosteric modulation of GABA-A receptors	Rapid onset; reliable short-term effect	Sedation, falls, cognitive impairment, tolerance and dependence; masking of hypoglycaemic warning symptoms [9,10]
SSRIs / SNRIs	Inhibit serotonin (± noradrenaline) reuptake	First-line for long-term use	Delayed onset; sexual dysfunction; some are associated with weight gain and altered glycaemic control [9]
Buspirone	5-HT1A partial agonism	Non-sedating; no dependence	Slow onset; modest efficacy; dosing frequency [9]
Pregabalin	α2δ ligand of voltage-gated calcium channels	Effective in generalised anxiety	Weight gain, oedema, dizziness; misuse potential [9]

Class	Main mechanism	Strengths	Limitations relevant to diabetes
Tricyclic antidepressants	Monoamine reuptake inhibition	Effective in some patients	Anticholinergic and cardiometabolic effects; poor tolerability

Two gaps emerge from this overview. None of the established drugs corrects the oxidative and inflammatory milieu shared by anxiety and diabetes, and several add to the metabolic burden. Hence the interest in agents that address upstream biology.

3.4 Natural products in anxiety

Plant-based medicines have a long history in anxiety management, and a review of preclinical studies has documented anxiolytic-like activity for a range of extracts and isolated compounds, including flavonoids, terpenoids and polyphenols [11]. The common weaknesses are inadequate standardisation, small studies and a lack of mechanistic follow-up. A compound such as lunularin, with a defined structure and measurable dose, offers an opportunity to avoid these problems.

4. Diabetes Mellitus and Glucose Homeostasis

4.1 Classification and epidemiology

The American Diabetes Association classifies diabetes into type 1, type 2, gestational and other specific types, with type 2 reflecting a progressive loss of adequate β-cell insulin secretion on the background of insulin resistance [5]. India carries one of the largest absolute burdens of diabetes in the world, and the disease increasingly affects younger adults [4]. The consequences extend beyond the classical micro- and macrovascular complications to cognitive dysfunction, depression and anxiety [6,7,28].

4.2 Normal glucose homeostasis

Blood glucose is held within a narrow range by the coordinated action of several organs. After a meal, rising glucose and incretin hormones stimulate insulin secretion from pancreatic β-cells. Insulin promotes glucose uptake in skeletal muscle and adipose tissue by translocating GLUT4 to the plasma membrane, increases hepatic glycogen synthesis and suppresses hepatic gluconeogenesis. In the fasting state, glucagon and counter-regulatory hormones, including cortisol and catecholamines, maintain glucose output from the liver [29].

The brain is not a passive consumer in this system. Hypothalamic neurons sense insulin, leptin and glucose, and relay signals that adjust hepatic glucose production, peripheral insulin sensitivity and food intake. Central nervous system control of glucose homeostasis is increasingly regarded as a therapeutic target in T2DM, and failure of this control is one of the ways in which brain dysfunction and metabolic dysfunction become intertwined [27].

4.3 Pathophysiology of type 2 diabetes

T2DM develops when β-cell compensation can no longer overcome insulin resistance. Obesity, physical inactivity, ectopic lipid deposition and chronic low-grade inflammation impair insulin signalling in liver, muscle and fat. Initially, β-cells increase insulin output. Over time, glucotoxicity, lipotoxicity, endoplasmic reticulum stress, islet amyloid deposition and oxidative damage cause β-cell dysfunction and loss, and fasting and postprandial glucose rise [29].

Oxidative stress holds a central position in this picture. In hyperglycaemia, excess substrate flux through the mitochondrial electron transport chain generates superoxide, which activates the polyol, hexosamine, protein kinase C and advanced glycation end-product pathways, a unifying mechanism proposed for diabetic complications [30]. β-cells express low levels of antioxidant enzymes and are particularly vulnerable. These same pathways operate in neurons and glia, which is why diabetes is associated with changes in brain structure and function [28,30].

4.4 Central nervous system complications

Diabetes is associated with accelerated cognitive decline and an increased risk of dementia. Proposed mechanisms include microvascular injury, impaired cerebral insulin signalling, advanced glycation, mitochondrial dysfunction, neuroinflammation, repeated hypoglycaemia and blood–brain barrier alterations [28]. In rodent models, STZ-induced diabetes has been reported to produce anxiety-like behaviour, impaired spatial learning and altered hippocampal morphology, which is why behavioural readouts are legitimately

included when testing candidate drugs in diabetic animals. A compound that improves glycaemia but leaves these changes untouched would be of limited value for diabetes-associated neurobehavioural complications, and so would be one that relieves anxiety while worsening glucose handling.

5. Shared Mechanisms Linking Anxiety and Impaired Glucose Homeostasis

The clinical co-occurrence of anxiety and T2DM has a mechanistic explanation. Several biological systems regulate both emotional reactivity and glucose metabolism, and when they are disturbed the two conditions reinforce each other. Understanding these nodes matters, because they define where a dual-acting drug could intervene.

5.1 HPA-axis hyperactivity and glucocorticoid excess

Chronic psychological stress and chronic anxiety sustain activation of the HPA axis. Elevated glucocorticoids antagonise insulin action in muscle and fat, stimulate hepatic gluconeogenesis, redistribute fat to the abdomen and impair pancreatic β-cell function [8,29]. In the brain, prolonged glucocorticoid exposure reduces dendritic complexity and BDNF expression in the hippocampus and prefrontal cortex while increasing amygdala excitability, which strengthens the very circuits that produce anxiety [8]. In diabetes, hyperglycaemia, hypoglycaemic episodes and the daily burden of disease management can act as chronic stressors, so the loop closes: stress worsens glucose control, and poor glucose control prolongs stress.

5.2 Oxidative stress

Hyperglycaemia increases mitochondrial superoxide production and activates the downstream damage pathways described by Brownlee [30]. In parallel, anxiety-like states in rodents are accompanied by increased malondialdehyde, reduced glutathione and lower activity of superoxide dismutase and catalase in the hippocampus and cortex, and human studies link oxidative damage markers to anxiety and mood disorders [24,25]. Oxidative stress is therefore both a consequence of metabolic disease and a driver of neuropsychiatric symptoms. It also damages insulin signalling directly, since reactive oxygen species activate stress kinases that phosphorylate insulin receptor substrates and blunt downstream signalling [29,30]. Antioxidant strategies are therefore attractive in this setting, although it should be noted that broad-spectrum antioxidant supplements have a poor track record in clinical trials. Compounds that also regulate signalling pathways, rather than simply scavenging radicals, may perform better.

5.3 Neuroinflammation and low-grade systemic inflammation

Adipose tissue inflammation in obesity and T2DM raises circulating interleukin-6, tumour necrosis factor-α and C-reactive protein. These mediators cross or signal across the blood–brain barrier and activate microglia, which in turn release cytokines and reactive species locally [26]. Cytokine signalling alters monoamine metabolism, reduces synaptic plasticity and promotes anxiety- and depression-like behaviour in animals. The same cytokines worsen peripheral insulin resistance, creating a second feed-forward loop. Several stilbenoids suppress nuclear factor-κB signalling and microglial activation in experimental models, and this is the best-characterised class-level neuroprotective mechanism [26,43].

5.4 Brain insulin signalling, BDNF and synaptic plasticity

Insulin receptors are abundant in the hippocampus, hypothalamus and cortex. Insulin signalling in neurons supports synaptic plasticity, neuronal survival and glucose utilisation, and brain insulin resistance is increasingly recognised in T2DM [27,28]. BDNF, acting through TrkB receptors, supports neurogenesis and synaptic strengthening, and is reduced in both chronic stress and diabetes. Agents that restore BDNF signalling and brain insulin sensitivity could therefore improve mood and cognition independently of glucose lowering, a possibility that makes combined behavioural and metabolic evaluation especially informative.

5.5 Neurotransmitter systems and glycaemia

GABAergic and monoaminergic systems also influence glucose regulation. Central serotonergic and

noradrenergic pathways modulate sympathetic outflow, hepatic glucose output and appetite, and many psychotropic drugs alter weight and glycaemia as a side effect [9,27]. An ideal dual-acting agent would modify these systems without causing metabolic harm.

Table 3: Convergent Pathways in Anxiety and T2DM and Potential Points of Intervention

Pathway	Effect on anxiety	Effect on glucose homeostasis	Potential stilbenoid / lunularin action (grade)
HPA-axis hyperactivity	Amygdala hyper-reactivity; hippocampal atrophy	Insulin resistance; increased gluconeogenesis	Attenuation of stress-induced corticosterone (class-based; inferred for lunularin)
Oxidative stress	Neuronal lipid peroxidation; impaired plasticity	β-cell and insulin-signalling damage	Radical scavenging; antioxidant enzyme induction (class-based; direct data limited)
Neuroinflammation	Microglial activation; altered monoamines	Cytokine-mediated insulin resistance	NF-κB inhibition; reduced cytokines (class-based)
Brain insulin / BDNF	Reduced plasticity and resilience	Central control of hepatic glucose output	Increased BDNF; improved insulin signalling (class-based; inferred)
AMPK / SIRT1 energy sensing	Mitochondrial resilience in neurons	Glucose uptake; reduced hepatic output	AMPK activation (class-based)
GABA / monoamines	Core anxiolytic targets	Autonomic and appetite regulation	GABA-A or MAO modulation (inferred)

6. Stilbenoids: Chemistry, Sources and Pharmacology

6.1 Classification and structure

Stilbenoids are a family of phenolic secondary metabolites characterised by a 1,2-diphenylethylene (stilbene) backbone, typically produced in response to infection, UV exposure or injury and therefore classed as phytoalexins [9,13,34]. The family includes monomeric stilbenes (resveratrol, pterostilbene, piceatannol), glycosides (piceid), oligomers (ε-viniferin) and the related dihydrostilbenes or bibenzyls, in which the central ethene bond is saturated [13,34,35]. Biosynthesis proceeds via the phenylpropanoid pathway, in which stilbene synthase condenses a coumaroyl-CoA starter unit with three malonyl-CoA units. Natural bibenzyls such as lunularin arise by reduction of a stilbene or, in liverworts, by decarboxylation of the dihydrostilbene carboxylic acid lunularic acid [16,37].

Structural variation within the family (number and position of hydroxyl groups, methylation, glycosylation, degree of unsaturation and prenylation) controls solubility, metabolic stability and biological activity [13,35,36]. Methylation, for instance, increases lipophilicity and protects against conjugation, which helps explain the better oral bioavailability of pterostilbene compared with resveratrol [15,36].

6.2 Natural distribution

Stilbenoids occur in grapes and wine, peanuts, berries, the heartwood of Pterocarpus species, pines, and in many medicinal plants and liverworts [13,34]. Bibenzyls are particularly abundant in the Orchidaceae, including Dendrobium and Gastrodia species used in traditional medicine for neurological and metabolic indications, as well as in bryophytes [16,38,39].

6.3 Pharmacological profile

The pharmacology of resveratrol is wide-ranging. In preclinical models it has antioxidant, anti-inflammatory, cardioprotective, neuroprotective, anti-ageing and metabolic effects, mediated through targets that include SIRT1, AMPK, PGC-1α, nuclear factor-κB, Nrf2 and phosphodiesterases [12,21,22,44,50]. Pterostilbene, the dimethylated analogue, shows comparable or superior activity in several models with higher oral bioavailability [15,36]. Both compounds reduce oxidative stress, improve insulin sensitivity and show neuroprotective actions in rodents [12,36,43].

However, the evidence must be read with care. The oral bioavailability of resveratrol in humans is below 1% for

the parent compound because of rapid sulfation and glucuronidation, even though absorption is high [14]. Many in vitro effects are seen at concentrations that are not reached in vivo, and the claim that resveratrol acts as a direct SIRT1 activator has been challenged [42]. Human trials have produced inconsistent results (Section 9). These caveats are central to the argument for examining metabolites and structural analogues, since the compounds that actually reach tissues may differ from the compound administered [17,18].

6.4 Structure–activity considerations

Three structural features distinguish lunularin from the better known stilbenoids. First, it lacks the central double bond, which gives its two aromatic rings rotational freedom and removes the extended conjugation of resveratrol. Second, it has only two phenolic hydroxyl groups (positions 3 and 4′), against three in resveratrol, which changes hydrogen-bonding capacity, conjugation sites and redox behaviour. Third, its lower molecular weight and absence of a rigid planar geometry may favour passage across biological membranes [16,36]. Whether these differences improve or reduce activity at specific targets is not known, and this uncertainty is precisely what warrants direct experimental testing.

Table 4: Comparison of Lunularin with Selected Stilbenoids

Compound	Class	Molecular formula	Molecular weight (g/mol)	Hydroxyl / methoxy groups	Central bond	Principal source
Resveratrol	Stilbene	C14H12O3	228.24	3 OH	Double	Grapes, peanuts, Polygonum species
Pterostilbene	Methylated stilbene	C16H16O3	256.29	1 OH, 2 OMe	Double	Blueberries, Pterocarpus marsupium
Dihydroresveratrol	Dihydrostilbene	C14H14O3	230.26	3 OH	Single	Gut-microbial metabolite of resveratrol
Lunularin	Dihydrostilbene (bibenzyl)	C14H14O2	214.26	2 OH	Single	Liverworts, orchids; gut-microbial metabolite

7. Lunularin: Chemistry, Occurrence and Metabolic Origin

7.1 Chemical identity

Lunularin (3,4′-dihydroxybibenzyl; 3-[2-(4-hydroxyphenyl)ethyl]phenol) is a dihydrostilbenoid with the molecular formula C14H14O2 and a molecular weight of 214.26 g/mol [16]. It is a phenolic solid, soluble in organic solvents such as ethanol, dimethyl sulfoxide and ethyl acetate and poorly soluble in water, which determines the vehicles and suspension agents required for oral dosing in animals. The two phenolic hydroxyls are the principal sites for hydrogen atom donation (antioxidant activity) and for phase II conjugation (sulfation and glucuronidation).

7.2 Natural occurrence

Lunularin was first associated with liverworts, notably *Lunularia cruciata*, where it forms through decarboxylation of lunularic acid, a growth regulator that is widely distributed in liverworts and that fulfils a role analogous to abscisic acid in higher plants [16,37]. Bibenzyl derivatives are a hallmark of bryophyte chemistry, and many show cytotoxic, antimicrobial, anti-inflammatory and neuroactive properties [16]. Orchid species, including Dendrobium and Gastrodia, are also rich in bibenzyls, and several of these medicinal plants have documented neuroprotective, sedative and anti-diabetic uses in traditional practice [38,39]. Reports of lunularin itself in orchids exist, but the amount and consistency of its occurrence should be verified for any given species and extraction method.

7.3 Lunularin as a gut-microbial metabolite of resveratrol

One reason lunularin has recently drawn attention is that it is a quantitatively important product of human gut bacteria. After oral intake, resveratrol that is not conjugated and absorbed is reduced by intestinal microbiota to dihydroresveratrol, which can then be

dehydroxylated to lunularin [17]. Individuals differ markedly in this capacity. Work on human metabolism of dietary resveratrol has described "lunularin producers" and "non-producers" as distinct metabotypes, which raises the question of whether microbial metabolites contribute to, or even explain, some of the inter-individual variability in responses to resveratrol supplements [18]. If lunularin is the form that circulates for long periods and reaches tissues, its pharmacology is not a curiosity but a necessary part of understanding stilbenoid biology in humans.

7.4 What is known about the biological activity of lunularin

The pharmacological literature on lunularin is thin. It has been examined mainly in phytochemical and metabolism studies, in screens of bryophyte and orchid constituents, and in work on resveratrol metabolites [16–18]. As a phenolic bibenzyl it is expected to scavenge free radicals, and related bibenzyls show anti-inflammatory and neuroprotective properties [16,38]. Comprehensive in vivo evaluation of anxiolytic or glucose-lowering activity has not, to our knowledge, been reported, and the evidence status in Table 5 should be read in that light.

Table 5: Evidence Status for Lunularin

Domain	Status	Basis
Chemical identity and occurrence	Established	Phytochemical studies [16,37]
Formation by human gut microbiota	Established	Metabolism studies [17,18]
Antioxidant activity	Plausible; limited direct data	Phenolic structure; bibenzyl class [16,38]
Anti-inflammatory / neuroprotective activity	Plausible; class-based	Bibenzyls and stilbenoids [13,38]
Anxiolytic activity in vivo	Not established	No comprehensive study identified
Antidiabetic activity in vivo	Not established	No comprehensive study identified
Pharmacokinetics and toxicity	Largely unknown	Inferred from resveratrol and metabolites [14,17]

8. Anxiolytic Potential of Stilbenoids and Lunularin

8.1 Evidence from stilbenoid class

The strongest behavioural data in the field relate to resveratrol and mood. In mice, trans-resveratrol shortened immobility in the forced swim and tail suspension tests, an effect accompanied by increased brain serotonin and noradrenaline and inhibition of monoamine oxidase A [19]. In a rat model of depression (olfactory bulbectomy), chronic resveratrol reversed behavioural deficits [20]. Reviews of resveratrol in neurological disease describe antioxidant, anti-inflammatory and neurotrophic actions that could plausibly support anxiolytic-like effects, although studies that specifically measure anxiety-like behaviour with validated paradigms are fewer and outcomes depend on dose, species and stress model [43,50]. For pterostilbene and bibenzyls from orchids, evidence is mainly neuroprotective and cognitive [36,38]. In short, the class provides a credible, but incomplete and heterogeneous, basis for anxiolytic hypotheses.

8.2 Proposed mechanisms for lunularin

We propose five mechanisms by which lunularin could reduce anxiety-like behaviour, ranked here by plausibility rather than by direct evidence.

(i) Attenuation of oxidative stress in limbic regions. As a phenolic hydrogen donor, lunularin may scavenge reactive oxygen species and spare endogenous antioxidants such as glutathione, as shown for resveratrol and related polyphenols [24,25,50]. Increased hippocampal and cortical antioxidant enzyme activity and reduced lipid peroxidation are measurable outcomes in a diabetic rat study.

(ii) Suppression of microglial activation and cytokine release. Stilbenoids restrain NF-κB-dependent transcription and microglial activation [26,43]. A bibenzyl with this property would reduce the neuroinflammatory component of anxiety, especially in diabetic brains.

(iii) Modulation of monoaminergic tone. Resveratrol raises serotonin and noradrenaline, partly through MAO inhibition [19]. Whether lunularin inhibits MAO or influences monoamine turnover is unknown, but its structure is consistent with such activity and the question is experimentally tractable.

(iv) Potential GABAergic modulation. Many polyphenols and bibenzyls act at the benzodiazepine site or elsewhere on the GABA-A receptor complex [23]. This is an inferred mechanism for lunularin and should be tested, for example with flumazenil antagonism in the EPM, rather than assumed.

(v) Restoration of BDNF and synaptic plasticity. By lowering oxidative and inflammatory load, and potentially via AMPK and SIRT1 pathways [21,22,40], lunularin might restore hippocampal BDNF, which would be expected to improve both anxiety-like behaviour and spatial learning.

Table 6: Proposed Anxiolytic Mechanisms of Lunularin and How Each Can Be Tested

Proposed mechanism	Grade	Suggested test
Antioxidant effect in brain	Class-based	Brain MDA, GSH, SOD, catalase
Anti-neuroinflammatory effect	Class-based	Brain TNF-α, IL-1β, IL-6; microglial staining
Monoaminergic modulation	Inferred	Brain serotonin and noradrenaline; MAO activity
GABA-A modulation	Inferred	EPM with flumazenil co-treatment; GABA assay
BDNF restoration	Inferred	Hippocampal BDNF (ELISA or immunohistochemistry)

8.3 Blood–brain barrier penetration

Anxiolytic activity requires central exposure. Compounds with molecular weight below about 450 Da, few hydrogen-bond donors and moderate lipophilicity typically cross the blood–brain barrier by passive diffusion. Lunularin (214.26 g/mol; two phenolic hydroxyl groups) falls within this range on structural grounds, and resveratrol and its analogues have been detected in rodent brain after oral or parenteral dosing [14,15,43]. Extensive first-pass conjugation may reduce the amount of free lunularin reaching the brain, so measurement of brain and plasma concentrations is an essential complement to behavioural testing and not an optional extra.

8.4 Separating anxiolysis from sedation and motor impairment

Behavioural readouts for anxiety are confounded by locomotor changes. A sedative drug can reduce exploration and mimic increased anxiety, while a stimulant can appear anxiolytic by increasing open-arm entries without any change in emotional state. Diazepam, the standard anxiolytic used in the proposed model, itself causes sedation and ataxia at higher doses [10,23]. A credible anxiolytic candidate must therefore increase open-arm exploration in the elevated plus maze without reducing locomotor counts in the actophotometer or latency to fall on the rotarod. This is why the behavioural battery proposed in Section 11 combines the EPM with locomotor and motor-coordination tests.

9. Antidiabetic Potential of Stilbenoids and Lunularin

9.1 Molecular targets in glucose regulation

AMPK. AMP-activated protein kinase is a cellular energy sensor that is activated when the AMP:ATP ratio rises. Activated AMPK increases glucose uptake in muscle through GLUT4 translocation, suppresses hepatic gluconeogenic enzyme expression, enhances fatty acid oxidation and inhibits lipogenesis, making it a central target for antidiabetic therapy [40]. Resveratrol activates AMPK in liver, muscle and other tissues, and this effect has been linked to improved insulin sensitivity and mitochondrial function [21,22].

SIRT1 and PGC-1α. In obese mice fed a high-fat diet, resveratrol improved insulin sensitivity, increased mitochondrial number and prolonged survival, and these benefits were linked to deacetylation and activation of PGC-1α through SIRT1 [21,41]. It has since been shown that resveratrol may activate AMPK and SIRT1 indirectly, for example through inhibition of cAMP phosphodiesterases [22], and that its action as a direct SIRT1 activator in cell-free assays may be an artefact of the fluorophore-labelled substrate used [42]. The

sensible reading is that stilbenoids engage the AMPK–SIRT1–PGC-1α energy-sensing network by more than one route, and that the exact mechanism for each compound must be determined experimentally.

Insulin signalling and GLUT4. Polyphenols can enhance phosphorylation of insulin receptor substrate-1 and Akt, increasing GLUT4 translocation, and can reduce the serine phosphorylation of insulin receptor substrates caused by inflammatory kinases [12,50]. By reducing oxidative and inflammatory stress, stilbenoids may restore insulin responsiveness in tissues rendered resistant.

β-cell protection. Because β-cells have weak antioxidant defences, they are vulnerable to reactive oxygen species generated by glucotoxicity and lipotoxicity, and also to the alkylating and nitric oxide-generating effects of streptozotocin [51]. Antioxidant and anti-inflammatory compounds protect β-cells in experimental diabetes, and histopathology of the pancreas is therefore an essential endpoint for any candidate [12,49].

Hepatic lipid and glucose metabolism. Suppression of hepatic gluconeogenesis and lipogenesis through AMPK, together with reduced hepatic steatosis, contributes to lower fasting glucose and triglycerides in animal studies of resveratrol [21,41].

9.2 Preclinical antidiabetic evidence for stilbenoids

In rodent models of diet-induced and genetic obesity, resveratrol improves insulin sensitivity, glucose tolerance and lipid profile [21,41]. Pterostilbene, isolated from the heartwood of *Pterocarpus marsupium*, was identified as an antihyperglycaemic principle that lowered blood glucose in streptozotocin-diabetic rats to an extent comparable to metformin in the same study [49].

Several reviews have collated further evidence for stilbenoids and bibenzyls in glucose and lipid metabolism, but experimental designs vary widely in model, dose, duration and endpoints, which limits direct comparison [12,44,50].

9.3 Clinical evidence for resveratrol: encouraging but inconsistent

Human data illustrate both the promise and the problems of stilbenoid pharmacology. In obese but otherwise healthy men, 30 days of 150 mg/day resveratrol lowered glucose, triglycerides, inflammatory markers and liver enzymes and improved an index of insulin sensitivity, with reduced sleeping metabolic rate, resembling the effects of calorie restriction [45]. By contrast, a four-week trial of 3 g/day in obese men found no improvement in insulin sensitivity measured by the hyperinsulinaemic–euglycaemic clamp [46]. In patients with T2DM receiving oral hypoglycaemic agents, 250 mg/day for three months improved glycated haemoglobin, systolic blood pressure and total cholesterol in a small trial [48]. A meta-analysis of randomised controlled trials found that resveratrol significantly improved glucose control and insulin sensitivity in people with diabetes, but not in those without it [47].

These results suggest that benefit is more likely in the diabetic than the non-diabetic state, that dose–response relationships may not be linear, and that variability between individuals, perhaps including gut microbial metabolism, could be a factor [17,18,47]. They also underline why a model of established T2DM, rather than normal animals, is the appropriate testing ground for a candidate such as lunularin.

Table 7: Selected Evidence for the Metabolic Effects of Resveratrol and Pterostilbene

Study type / model	Compound and dose	Principal metabolic finding	Reference
High-fat-diet mice	Resveratrol, 22 mg/kg/day (study range)	Improved insulin sensitivity; increased survival	[41]
High-fat-diet mice	Resveratrol, high dose	Increased mitochondrial function via SIRT1 and PGC-1α	[21]
STZ-diabetic rats	Pterostilbene from *P. marsupium*	Antihyperglycaemic activity, comparable to metformin	[49]
Obese men, 30 days	Resveratrol, 150 mg/day	Improved metabolic profile, reduced hepatic fat	[45]
Obese men, 4 weeks	Resveratrol, 3 g/day	No improvement in clamp-measured insulin sensitivity	[46]

Study type / model	Compound and dose	Principal metabolic finding	Reference
Patients with T2DM, 3 months	Resveratrol, 250 mg/day	Lower HbA1c and blood pressure	[48]
Meta-analysis of RCTs	Resveratrol, various	Better glucose control and insulin sensitivity in diabetes only	[47]

9.4 Hypothesis for lunularin

No antidiabetic study of lunularin has been identified. A reasonable working hypothesis is that, as a resveratrol-derived and structurally related bibenzyl, lunularin may (a) reduce oxidative stress in pancreatic, hepatic and brain tissue, (b) activate AMPK-dependent pathways, and (c) improve insulin sensitivity, resulting in lower fasting glucose and improved lipid profile. These effects should be tested directly, and potency relative to resveratrol is not predictable from structure alone. Importantly, if lunularin is the persisting circulating form after resveratrol intake, then testing it directly may help explain the metabolic effects seen with resveratrol supplements in people who produce it [17,18].

10. An Integrated Dual-Action Hypothesis

Pulling the preceding sections together, we propose that lunularin could act on anxiety and glucose homeostasis through overlapping pathways, as depicted in the following causal chain: reduction of oxidative stress and inflammation, activation of AMPK-related energy sensing, improvement in insulin signalling and β-cell survival, and, as a result, a lower glycaemic and stress burden, which in turn lowers HPA-axis drive and supports hippocampal and amygdala function. The central point of the hypothesis is that a single mechanism, restoration of redox and inflammatory balance, simultaneously relieves peripheral metabolic stress and central neuronal stress, and that the two benefits reinforce one another.

The hypothesis generates falsifiable predictions, summarised in Table 8. Importantly, it distinguishes between the possibility that anxiolysis is secondary to improved glycaemia (in which case behavioural effects should track glucose changes) and the possibility that lunularin has independent central actions (in which case behavioural effects should appear at doses with limited effect on glucose, or should not correlate with glucose within groups).

Table 8: Predictions of the Dual-Action Hypothesis and Interpretation

Observation	Interpretation
Lower FBG and improved lipid profile, with higher open-arm time in the EPM and unchanged locomotor counts	Supports dual action without sedation
Improved EPM behaviour at doses that do not change glucose	Suggests independent central anxiolytic mechanism
Lower glucose but no behavioural change	Antidiabetic effect without central benefit; anxiolytic hypothesis not supported
Behavioural change accompanied by reduced locomotor counts or shorter rotarod latency	Suggests sedation or motor impairment, not true anxiolysis
Improved MWM performance together with higher hippocampal antioxidant status	Supports neuroprotective action in the diabetic brain
Dose-dependent improvements across 25, 50 and 100 mg/kg	Supports a pharmacological dose–response relationship
Preserved islet architecture on histology	Supports β-cell protection

11. Preclinical Evaluation Framework

11.1 Choice of disease model: STZ–nicotinamide diabetic rat

Streptozotocin enters pancreatic β-cells through the GLUT2 transporter and causes cell death through DNA alkylation, activation of poly (ADP-ribose) polymerase, depletion of NAD+ and generation of reactive oxygen and nitrogen species [51]. Nicotinamide, given shortly before STZ, partly protects β-cells by supporting NAD+ levels and inhibiting PARP, so that a fraction of functional β-cell mass survives. The resulting phenotype is moderate, stable hyperglycaemia with impaired glucose-stimulated insulin

secretion and relatively preserved insulin content, which resembles non-insulin-dependent diabetes more closely than STZ alone [33]. Reviews of the model recommend careful attention to strain, nicotinamide and STZ doses, fasting state and timing, because outcomes vary considerably between laboratories [31,32]. Nicotinamide and STZ doses reported in the literature vary substantially across studies (for example nicotinamide from roughly 100 to over 200 mg/kg and STZ from about 45 to 65 mg/kg), and the severity of hyperglycaemia should be confirmed in each cohort [31,33].

The model also has recognised limitations. It reflects β-cell deficiency more than the primary insulin resistance of human T2DM, STZ has non-pancreatic toxicity (hepatic and renal), and behavioural changes may reflect general malaise as well as diabetic neurobiology. These points argue for rigorous controls and body-weight monitoring.

11.2 Experimental design

The design proposed for the research programme underlying this review uses adult male albino Wistar rats (150–200 g) housed under standard conditions in accordance with CPCSEA guidelines and with prior approval from the Institutional Animal Ethics Committee. Diabetes is induced by intraperitoneal nicotinamide (120 mg/kg), given 15 minutes before intraperitoneal STZ (55 mg/kg, in cold citrate buffer, pH 4.5) to overnight-fasted animals. Fasting blood glucose is monitored at day 0, 3 and 7 and then weekly to day 28, and animals with FBG below 200 mg/dL are excluded. Lunularin is administered orally at 25, 50 and 100 mg/kg, and glibenclamide and diazepam serve as reference drugs.

Table 9: Experimental Groups (N = 6 per Group)

Group	Designation	Treatment	Dose and route
I	Normal control	Vehicle only (CMC)	p.o., daily
II	Diabetic control	STZ + NA	STZ 55 mg/kg i.p.; NA 120 mg/kg i.p.
III	Standard antidiabetic	STZ + NA + glibenclamide	5 mg/kg p.o.
IV	Standard anxiolytic	STZ + NA + diazepam	2 mg/kg i.p.
V	Lunularin low	STZ + NA + lunularin	25 mg/kg p.o.
VI	Lunularin mid	STZ + NA + lunularin	50 mg/kg p.o.
VII	Lunularin high	STZ + NA + lunularin	100 mg/kg p.o.

Several design refinements deserve consideration. First, a normal-control group treated with the highest lunularin dose would separate drug effects on behaviour in healthy animals from effects specific to the diabetic state. Second, the diabetic control group should receive the same vehicle and route as treated groups. Third, assessors should be blinded to group allocation, animals should be randomised, and a sample size justification should be reported. Groups of six are common in exploratory pharmacology but offer limited power for behavioural endpoints, which are inherently variable [58,59]. Reporting should follow the ARRIVE guidelines [59].

11.3 Dose selection and translation

The three doses (25, 50 and 100 mg/kg) allow dose–response assessment and identification of the minimum effective dose. Using body-surface-area normalisation with Km factors of 6 for rats and 37 for humans, the corresponding human equivalent doses are approximately 4, 8 and 16 mg/kg, or about 240, 490 and 970 mg for a 60 kg adult [60]. These figures are theoretical, since lunularin has not undergone human testing, but they serve to show that the top dose corresponds to a gram-range human dose, which may be difficult to deliver and would require good safety margins.

11.4 Behavioural test battery

Behavioural tests have to be selected and sequenced carefully, because each is influenced by prior handling and stress. The battery used here pairs a primary anxiety test with tests that exclude confounders.

Elevated plus maze (EPM). The EPM exploits the conflict between the rodent's drive to explore a novel environment and its aversion to open, elevated spaces. Anxiolytic drugs increase the proportion of entries into

and time spent on open arms [52,53]. The classic validation relied on the ratio of open to closed arm entries, and later work emphasised that closed-arm entries provide a useful index of general locomotion. Standard measures are open-arm entries, closed-arm entries and time in each arm over a five-minute session. The maze should be cleaned with 70% ethanol between animals to remove olfactory cues.

Actophotometer (locomotor activity). Locomotor activity measured by infrared beam interruptions confirms that behavioural findings are not a by-product of sedation or hyperactivity [57,58]. Unchanged counts with increased open-arm exploration point to a genuine anxiolytic action.

Rotarod. The rotarod tests motor coordination and balance by measuring latency to fall from a rotating rod, a method introduced for detecting neurological deficit in rodents [56]. Maintenance of performance at an effective dose indicates a favourable therapeutic window, which is especially relevant when benchmarking against diazepam.

Morris water maze (MWM). The MWM measures hippocampus-dependent spatial learning and memory through escape latency to a hidden platform and, in the probe trial, time spent in the target quadrant and platform crossings [54,55]. Because diabetes impairs hippocampal function, MWM performance supplies a cognitive readout of neuroprotection. Water temperature, cue placement, and swim speed must be controlled, as motor impairment or visual deficits can confound escape latency.

Table 10: Behavioural Tests, Parameters and Interpretation

Test	Domain	Primary parameters	Interpretation of an effective compound
Elevated plus maze	Anxiety-like behaviour	Open and closed arm entries; time in arms	Increased open-arm entries and time [52,53]
Actophotometer	Locomotor activity	Total activity counts	No significant change (excludes sedation or stimulation) [57]
Rotarod	Motor coordination	Latency to fall	Maintained or improved latency [56]
Morris water maze	Spatial learning and memory	Escape latency; target quadrant time; platform crossings	Shorter latency; more time and crossings in target quadrant [54,55]

11.5 Biochemical and histopathological endpoints

Biochemical assessment includes fasting blood glucose, lipid profile (total cholesterol, triglycerides, HDL, LDL), liver function tests (ALT, AST, ALP, bilirubin) and kidney function tests (urea, creatinine). The liver and kidney panels double as safety markers, which is important given STZ toxicity and the need to confirm that lunularin does not add organ injury. Consideration should be given to adding HbA1c, fasting insulin with HOMA-IR, and tissue oxidative stress and inflammatory markers (MDA, GSH, SOD, catalase, TNF-α, IL-6) in pancreas, liver and brain, so that mechanistic claims can be supported.

Histopathology of the pancreas (islet architecture and β-cell preservation), liver (steatosis, necrosis), kidney (glomerular and tubular changes) and brain (hippocampal neuronal integrity) provides structural confirmation of functional changes. Scoring should be blinded and semi-quantitative.

11.6 Statistical considerations

Continuous outcomes are usually analysed with one-way analysis of variance followed by a suitable post hoc test (Tukey for all pairwise comparisons or Dunnett for comparison with the diabetic control), and repeated-measures designs, such as MWM acquisition days or weekly glucose, with two-way repeated-measures ANOVA. Non-parametric tests are needed when assumptions are violated. Correlation analysis between FBG and behavioural parameters within the diabetic groups can help address whether anxiolysis follows glycaemic improvement or stands apart from it, which is the central question posed in Section 10.

12. Pharmacokinetics, Safety and Formulation Challenges

12.1 Absorption, metabolism and the problem of conjugation

Resveratrol is well absorbed but extensively conjugated in enterocytes and liver, leaving very little free parent compound in plasma [14]. Most circulating material consists of glucuronide and sulfate conjugates, which may act as a reservoir that is deconjugated in tissues [14,44]. Pterostilbene, with fewer free hydroxyl groups, shows higher bioavailability in rats [15]. Lunularin has two phenolic hydroxyls available for conjugation and is therefore likely to be subject to similar first-pass metabolism, although this has to be established experimentally. Gut microbial transformation adds another layer, because intestinal bacteria generate lunularin from dietary resveratrol and may also further metabolise administered lunularin [17,18].

12.2 Formulation

Lunularin is lipophilic and poorly water soluble, and in rodent studies it can be administered as a suspension in carboxymethylcellulose (CMC), with a small proportion of a co-solvent such as DMSO if required. The vehicle must be tested alone, because solvents influence behaviour, and the final DMSO concentration should be kept low. Approaches used for related polyphenols to improve exposure include nanoparticles, lipid-based systems, cyclodextrin complexes and co-administration with absorption enhancers [44,50]. These strategies should be considered only after proof of efficacy of the free compound has been obtained.

12.3 Safety and toxicology

No formal toxicity data for lunularin have been identified. Acute oral toxicity should be evaluated according to the relevant OECD guideline before pharmacology studies, followed by repeated-dose studies if efficacy is shown. Safety questions of particular relevance include hepatic and renal effects (which can be monitored with the proposed panels), hypoglycaemia, particularly in combination with sulfonylureas, effects on cytochrome P450 enzymes and transporters (relevant because many diabetic patients take multiple drugs), and potential endocrine activity, because many stilbenoids and bibenzyls bind oestrogen receptors in vitro [12,50]. The comparison with glibenclamide and diazepam in the proposed design provides an initial benchmark for efficacy and for undesirable effects such as hypoglycaemia and sedation.

12.4 Gut microbiota as a source of variability

Because the capacity to produce lunularin from resveratrol differs between individuals [18], microbiota composition might influence both exposure and response to stilbenoid-rich diets and supplements. In rats, the microbiome also differs from humans, and diabetes itself alters gut microbial composition, so the interplay between lunularin and the microbiota in the STZ–NA model is an open question worthy of study.

13. Critical Appraisal, Research Gaps and Translational Barriers

13.1 Strength and weakness of the current evidence

The case for lunularin rests on three pillars: the shared biology of anxiety and T2DM, the wide pharmacological activity of the stilbenoid class, and the structural and metabolic features that make lunularin a distinctive member of that class. Each pillar has weaknesses. The shared biology is well supported, but the direction of causality between glycaemic control and anxiety remains partly unresolved. Class-level data are abundant, but they derive mainly from resveratrol, whose pharmacology is complicated by low bioavailability, contested targets and mixed human trial outcomes [14,42,46,47]. The data specific to lunularin are limited to chemistry, occurrence and microbial formation [16–18].

This imbalance has two implications. First, readers should resist the temptation to treat resveratrol findings as lunularin findings; saturating the central bond and removing one hydroxyl group may change target selectivity, potency and metabolic fate in ways that cannot be predicted. Second, there is a genuine opportunity: because so little has been done, even a well-designed dose-ranging study in a validated model would meaningfully add to the literature.

13.2 Key research gaps

Table 11: Priority Gaps and Suggested Studies

Gap	Why it matters	Suggested approach
No in vivo anxiolytic data for lunularin	Central hypothesis is untested	Dose-ranging EPM with locomotor and rotarod controls in normal and diabetic rats
No in vivo antidiabetic data	Dual-action claim depends on it	STZ–NA model with FBG, HbA1c, insulin, lipids and histology
Mechanism unknown	Needed to distinguish true pharmacology from nonspecific antioxidant effects	AMPK phosphorylation, oxidative stress markers, cytokines, BDNF, MAO and GABA-A assays
Pharmacokinetics and brain exposure	Anxiolytic action needs central availability	Plasma and brain LC–MS/MS after oral dosing; metabolite profiling
Toxicity not characterised	Prerequisite to any translational work	Acute and repeated-dose toxicity with haematology, biochemistry and histopathology
Interaction with standard drugs	Diabetic patients are polymedicated	Combination studies with glibenclamide, metformin and SSRIs; CYP inhibition screens
Role of microbial production in humans	May explain variable responses to resveratrol	Metabotype-stratified clinical and microbiome studies [18]

13.3 Methodological cautions

Several cautions follow from experience with natural-product pharmacology. Behavioural tests in rodents are sensitive to handling, time of day, housing, noise, light intensity and experimenter, and poor control of these variables is a major reason for non-replication [57,58]. Natural products can generate false positives in biochemical assays through nonspecific redox or aggregation effects, so activity in a cell-free assay should always be confirmed in cells and animals. Single-dose or single-endpoint conclusions invite over-interpretation; consistent dose–response across several independent endpoints is much more persuasive. Finally, reporting standards such as the ARRIVE guidelines should be followed so that studies can be evaluated and replicated [59].

13.4 Translational barriers

Translation faces scientific, practical and regulatory hurdles. Anxiety in rodents is modelled by approach–avoidance conflict tests whose predictive validity for human generalised anxiety is imperfect, and many compounds effective in rodents fail in the clinic [58]. Species differences in drug metabolism and in gut microbiota affect the exposure to lunularin and its metabolites [17,18]. Human equivalent doses calculated from the highest rodent dose are in the gram range [60], so potency and formulation will need to be improved. Supply is a further issue, since lunularin is not abundant in common foods, and large-scale isolation from liverworts or orchids is unlikely to be viable; chemical synthesis or biotransformation from resveratrol by microbial cultures would be needed. Finally, as a natural phenol with no prior regulatory history, lunularin would be handled as a new chemical entity, and would need the full toxicology package.

14. Future Perspectives

From phenotype to mechanism. If lunularin shows activity in the STZ–NA model, the next step is to find out how. Receptor-binding and electrophysiological studies on GABA-A receptors, enzyme assays for MAO-A and MAO-B, and measurement of AMPK, SIRT1, Nrf2 and NF-κB signalling in brain and peripheral tissues would show whether activity is mediated through specific targets or through general redox effects [19,21,22,40].

Broader models. The STZ–NA model should be complemented by models closer to the human insulin-resistant state, such as high-fat diet combined with low-dose STZ, and by chronic stress paradigms such as chronic unpredictable mild stress. Both sexes should be studied, since female rodents differ in HPA-axis reactivity, EPM behaviour and glycaemic responses, and most of the older literature used males only [53].

Structure–activity optimisation. Comparative testing of lunularin, dihydroresveratrol, resveratrol and methylated or halogenated analogues would clarify which features drive CNS activity and metabolic effects. A medicinal chemistry programme based on the bibenzyl scaffold could aim to improve potency, metabolic stability and brain penetration [13,35,36].

Pharmacokinetic–pharmacodynamic integration. Correlating brain and plasma concentrations with behavioural and glycaemic outcomes would establish exposure–response relationships and support rational dose selection for subsequent studies [14,15].

Delivery systems. Nano-formulations, lipid-based carriers and cyclodextrin complexes have improved exposure for other polyphenols and might help overcome the extensive conjugation of lunularin, provided the added complexity is justified by demonstrated efficacy [44,50].

Microbiome-informed pharmacology. Because gut bacteria generate lunularin from resveratrol, and individuals differ in this capacity, human studies that stratify participants by metabotype may show whether lunularin explains part of the variable response to resveratrol and whether supplementation with lunularin itself bypasses this variability [17,18].

Combination therapy. Lunularin might be used as an adjunct that reduces the dose of conventional agents and limits their side effects, for example by enabling lower doses of anxiolytics or antidiabetics. Interaction studies would be needed to ensure no pharmacokinetic or pharmacodynamic hazards [9,10].

CONCLUSION

Anxiety and type 2 diabetes share a network of mechanisms, including HPA-axis dysregulation, oxidative stress, neuroinflammation and impaired insulin signalling, that justifies the search for agents active in both conditions. Stilbenoids offer a rich scaffold for this purpose, and the preclinical literature on resveratrol and pterostilbene shows antioxidant, anti-inflammatory, neuroprotective and metabolic effects, albeit with significant caveats about bioavailability, mechanism and human reproducibility.

Lunularin occupies an unusual position in this field. It is chemically defined, naturally occurring in plants and formed in the human gut, and it has structural features that suggest favourable membrane permeability, but it has barely been studied pharmacologically. Neither its anxiolytic nor its antidiabetic potential has been established. The hypothesis advanced here, that restoration of redox and inflammatory balance could improve both brain and metabolic outcomes, is plausible and testable rather than proven.

A stepwise programme is therefore proposed: a dose-ranging study in the STZ–NA rat model with a behavioural battery that separates anxiolysis from sedation, biochemical and histopathological confirmation of glycaemic effects and organ safety, followed by mechanistic, pharmacokinetic and toxicological work. Whatever the outcome, the results will help establish whether dihydrostilbenes such as lunularin deserve a place alongside resveratrol and pterostilbene in the search for therapies for diabetes-associated neurobehavioural complications.

Conflict of interest.

The authors declare no conflict of interest.

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