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Physiological and Ecological Implications of Co-occurring Ivabradine and Antidiabetic Agents in Mammalian Fauna

Sri Venkatesh Uriti*[1], Acharyulu MLN[2], and Pattnaik Gurudatta[3]

[1]*Department of Pharmacy, Centurion University of Technology and Management, Vizianagaram, Andhra Pradesh 535003, India*
[2]*Department of Chemistry, Centurion University of Technology and Management, Vizianagaram, Andhra Pradesh 535003, Inida*
[3]*Department of Pharmacy, School of Pharmacy and Life Sciences, CUTM, Odisha, India*

ABSTRACT

Pharmaceutical residues in terrestrial ecosystems pose physiological challenges to wild mammalian fauna. The co-occurrence of cardiovascular modulators, such as the hyperpolarization-activated cyclic nucleotide-gated (If) channel blocker ivabradine, alongside oral hypoglycemic agents like metformin in habitats alters the metabolic and cardiovascular homeostatic mechanisms of non-target species. Wild rodent populations, particularly within the family Muridae, frequently inhabit anthropogenically impacted zones where they ingest bioaccumulative xenobiotics through contaminated food and water sources. Laboratory baselines, specifically streptozotocin-induced diabetic rodent models, show that metabolic dysfunction induces profound myocardial and vascular remodeling, characterized by autonomic imbalance and accelerated oxidative stress. The concurrent administration of ivabradine and antidiabetic agents in controlled cohorts mitigates heart rate elevation, preserves endothelial integrity, and normalizes glycemic fluctuations. Translating these pharmacological synergies to wild populations requires a multi-trophic perspective. Chronic exposure to sublethal therapeutic mixtures in natural environments perturbs natural adaptive thermogenesis, foraging behaviors, and predator-avoidance responses of wild rodents. The physiological alterations observed in laboratory trials serve as a predictive matrix for assessing ecological risk. Evaluating these mammalian responses at the individual and population levels reveals how chronic xenobiotic exposure compromises wildlife fitness and ecosystem-level resilience.

Keywords: *Ecopharmacology, Ivabradine, Metformin, Muridae, Streptozotocin.*

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Corresponding Author: *Sri Venkatesh Uriti*

E-mail Address: *venkateshbalaji230@gmail.com*

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1. Introduction

The proliferation of human pharmaceuticals in global ecosystems represents a significant threat to wildlife preservation and habitat stability [1]. Active pharmaceutical ingredients enter terrestrial and aquatic environments through multiple pathways, primarily driven by inefficient wastewater treatment processes, agricultural runoff, and the disposal of unused medications [2]. Sewage treatment plants are designed to remove conventional organic matter and suspended solids but frequently fail to eliminate polar organic micro-pollutants, including cardiovascular therapies and antidiabetic medications [3]. Consequently, treated effluents discharged into local waterways introduce persistent concentrations of these bioactive compounds into aquatic systems. Terrestrial ecosystems experience contamination through the application of biosolids as agricultural fertilizers and the use of reclaimed wastewater for irrigation [4]. These practices deposit pharmaceutical residues directly onto surface soils, facilitating bioaccumulation in terrestrial food webs, starting from soil macroinvertebrates to apex predators.

Among the diverse classes of contaminants, cardiovascular drugs and oral hypoglycemic agents are increasingly co-detected in suburban and agricultural watersheds [5].

The global rise in metabolic syndrome and type 2 diabetes has led to high prescription rates for combination therapies, including the If channel blocker ivabradine and biguanides like metformin [6]. Due to their high water solubility and resistance to rapid biodegradation, these compounds persist in environmental matrices for extended periods. Metformin, for instance, frequently occurs in surface waters at microgram-per-liter concentrations, while ivabradine residues are increasingly documented in municipal effluents [7]. The concurrent presence of these agents exposes wild fauna to complex chemical mixtures. The physiological consequences of such multi-drug exposure remain poorly characterized, as traditional ecotoxicological assessments focus primarily on single-compound exposures rather than synergistic chemical cocktails.

Wild rodents belonging to the family Muridae, including the brown rat (*Rattus norvegicus*) and the wood mouse (*Apodemus sylvaticus*), serve as ideal bioindicators for assessing the impact of environmental contaminants [8].

These species occupy central positions in terrestrial food webs, acting as primary consumers of seeds, vegetation, and invertebrates, while serving as a fundamental food source for raptors and mammalian carnivores [9]. Because of their close association with agricultural lands and urban boundaries, murid rodents are exposed to elevated concentrations of anthropogenic waste, including pharmaceutical residues. Their high metabolic rates, rapid reproductive cycles, and limited home ranges ensure that any physiological or genetic alterations observed in these populations directly reflect the localized chemical pressures of their immediate habitat [10]. Consequently, monitoring murid populations offers a reliable methodology for evaluating the bioaccumulative potential and ecotoxicity of pharmaceutical mixtures in real-world scenarios.

$$\text{Bioaccumulation Factor (BAF)} = \frac{C_{\text{organism}}}{C_{\text{environment}}}$$

While laboratory-bred Sprague-Dawley or Wistar rats share genetic lineage with wild *Rattus norvegicus*, profound physiological differences exist due to generations of controlled breeding [11]. Laboratory rodents live in pathogen-free, thermoneutral environments with ad libitum access to standardized diets, resulting in lower baseline physiological variability [12]. In contrast, wild murids must cope with fluctuating ambient temperatures, seasonal food scarcity, pathogen exposure, and predation pressures. These natural stressors demand highly responsive autonomic and metabolic systems. Consequently, when wild rodents are exposed to xenobiotics that alter cardiovascular parameters or blood glucose regulation, the ecological consequences are far more severe than the minor variations observed in a controlled laboratory setting. Laboratory-derived data must therefore be interpreted with careful consideration of these environmental stressors to prevent underestimating ecological risks.

Table 1: Baseline Metrics of Laboratory vs. Wild Rodents (Family Muridae)

Parameter / Dimension	Laboratory Rodents (e.g., *Rattus norvegicus* Sprague-Dawley)	Wild Murids (e.g., *Apodemus sylvaticus*, Wild *R. norvegicus*)	Translational & Ecopharmacological Vulnerability
Environmental Temperature	Strictly thermoneutral (20 - 24°C); minimal metabolic allocation for heat conservation.	Seasonally fluctuating; highly dependent on non-shivering thermogenesis (NST).	Xenobiotics that impair brown adipose tissue (BAT) function (e.g., metformin) pose severe hypothermic risks to wild populations.
Nutritional Dynamics	Standardized diet *ad libitum*; stable blood glucose baselines.	Patchy, seasonal food availability; high foraging energy expenditure.	Fluctuations in blood glucose due to antidiabetic residues cause neuroglycopenic cognitive impairment, degrading foraging efficiency.
Autonomic Control & HRV	Lower baseline sympathetic drive; moderate heart rate variability (HRV).	High sympathovagal dynamism; elevated baseline HRV indicating adaptive resilience.	Artificial slowing of sinoatrial pacemaker current (I_f) by ivabradine reduces heart rate responsiveness to acute ecological stressors.
Predation & Pathogen Pressures	Pathogen-free environment; zero predatory stress.	High pathogen load; constant risk of predation demanding acute flight-or-flight responses.	Cardiovascular or metabolic constraints compromise muscle endurance, exponentially increasing predation mortality.

2. Pathophysiological Baselines

2.1. Streptozotocin-Induced Diabetes as a Proxy for Metabolic Dysfunction

2.1.1. Mechanism of Beta-Cell Destruction and Hyperglycemia

In pharmacological research, the administration of streptozotocin is the standard protocol for inducing diabetic states in rodent models [13]. Streptozotocin is a glucosamine-nitrosourea compound that targets pancreatic islet β-cells via the glucose transporter 2 (GLUT2) receptor [14]. Once internalized, the molecule undergoes rapid intracellular decomposition, releasing highly reactive carbonium radicals that alkylate genomic DNA. This DNA damage triggers the overactivation of poly(ADP-ribose) polymerase-1 (PARP-1), depleting cellular nicotinamide adenine dinucleotide (NAD^+) and adenosine triphosphate (ATP) pools, ultimately culminating in necrotic cell death of the -cells.

The resulting insulin deficiency leads to persistent hyperglycemia, mimicking the clinical manifestation of advanced diabetes mellitus. In wild populations, metabolic disorders resembling this state can arise from consuming high-energy anthropogenic waste, agricultural runoffs rich in endocrine disruptors, or genetic mutations within isolated populations [15].

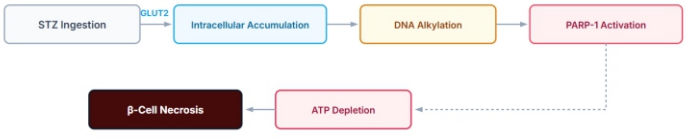

Figure 1: Streptozotocin-Induced Beta-Cell Destruction

2.1.2. Cardiovascular Consequences of Chronically Elevated Glucose

Persistent hyperglycemia initiates a cascade of cardiovascular complications in mammalian systems. Elevated circulating glucose levels promote the non-enzymatic glycosylation of structural proteins, generating advanced glycation end-products (AGEs) [16]. These AGEs cross-link collagen fibers within the arterial walls and myocardial interstitium, increasing vascular stiffness and ventricular diastolic dysfunction. Furthermore, the binding of AGEs to their specific receptors (RAGE) on endothelial cells triggers the upregulation of nuclear factor kappa B (NF-κB), driving chronic vascular inflammation and the overproduction of reactive oxygen species (ROS) via NADPH oxidase activation [17].

In laboratory models, this metabolic state leads to diabetic cardiomyopathy, characterized by microvascular rarefaction, interstitial fibrosis, and impaired cardiac output. For a wild rodent, these physical limitations directly translate to reduced physical endurance, compromised foraging capacity, and increased vulnerability to predation.

2.2. Mechanism of Action of Co-administered Therapeutics

2.2.1. Ivabradine: Selective If Channel Inhibition and Cardioprotection

Ivabradine is a highly selective therapeutic agent designed to reduce heart rate without altering myocardial contractility, intra-cardiac conduction, or systemic blood pressure [18]. The drug exerts its physiological effects by binding to the intracellular pore of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, specifically the HCN4 isoform predominant in the sinoatrial node.

By blocking the mixed sodium-potassium inward current, known as the pacemaker current (If), ivabradine prolongs the diastolic depolarization phase, thereby reducing the firing frequency of the sinoatrial node.

$$I_f = g_f \cdot (V_m - E_f)$$

Where gf represents the channel conductance, Vm is the membrane potential, and Ef is the reversal potential of the channel. In diabetic rats, heart rate reduction achieved through ivabradine administration alleviates myocardial oxygen demand, attenuates oxidative stress, and preserves coronary microvascular perfusion, offering a protective mechanism against diabetic cardiovascular decline [19].

Table 2: Multi-Drug Pharmacodynamics and Translational Ecological Vulnerabilities

Therapeutic Agent	Primary Molecular Target	Clinical / Laboratory Intended Effect	Translational Ecological Liability in Wild Prey
Ivabradine	Sinoatrial node HCN4 channels (pacemaker current, I_f)	Selective heart rate reduction; preservation of myocardial oxygen demand.	Establishes a ceiling on maximum heart rate; prevents the hemodynamic scaling required for explosive predator-evasion burst activity.
Metformin	Hepatocyte AMPK activation; Mitochondrial Complex I inhibition	Downregulated gluconeogenesis; increased peripheral glucose uptake; lower HbA1c.	Restricts rapid glycogenolysis and gluconeogenesis; limits cellular respiration substrates needed during prolonged escape and cold stress.
Sulfonylureas	Pancreatic β-cell ATP-sensitive potassium (K_{ATP}) channels	Depolarization-induced insulin secretion to correct chronic hyperglycemia.	Induces unpredictable hypoglycemia under food-scarce conditions; triggers metabolic exhaustion and neuroglycopenia.

2.2.2. Synergistic Interactions with Biguanides and Sulfonylureas

When combined with antidiabetic agents, ivabradine displays distinct physiological interactions. Biguanides, such as metformin, lower circulating glucose by activating adenosine monophosphate-activated protein kinase (AMPK) in hepatocytes, which downregulates key gluconeogenic enzymes and increases peripheral glucose disposal [20]. Sulfonylureas, conversely, promote insulin release by blocking ATP-sensitive potassium (KATP) channels on pancreatic -cell membranes, inducing depolarization and subsequent calcium influx.

The co-administration of ivabradine and these antidiabetic agents in streptozotocin-induced diabetic rats produces a dual therapeutic effect. While the antidiabetic agents restore glycemic balance and reduce vascular inflammation, ivabradine targets the elevated heart rates associated with autonomic neuropathy. This combined action helps restore normal vascular endothelial function, reduce systemic arterial stiffness, and optimize cardiac efficiency, demonstrating how multi-drug regimens can mitigate complex metabolic and cardiovascular disorders.

3. Comparative Ecophysiology of Chronic Xenobiotic Exposure

3.1. Disruption of Thermoregulation and Metabolic Homeostasis

3.1.1. Non-shivering Thermogenesis and Brown Adipose Tissue (BAT) Dysfunction

For wild murid rodents, survival in temperate or fluctuating climates depends on non-shivering thermogenesis, a metabolic process localized within brown adipose tissue (BAT) [21]. This pathway is mediated by the sympathetic nervous system, which releases norepinephrine to activate β3-adrenergic receptors, subsequently upregulating uncoupling protein 1 (UCP1) on the inner mitochondrial membrane. The presence of UCP1 dissipates the proton motive force across the mitochondrial membrane, generating heat rather than adenosine triphosphate (ATP).

Chronic exposure to environmental mixtures containing metformin and ivabradine compromises this critical survival mechanism. Metformin inhibits Complex I of the mitochondrial electron transport chain, which directly limits the proton gradient required for sustained uncoupling activity within BAT adipocytes [22].

Simultaneously, ivabradine, through its selective slowing of sinoatrial pacemaker current (If), reduces the circulatory rate required to distribute metabolically generated heat from BAT depots to the systemic core. The combination of these agents alters the metabolic capacity of brown adipocytes, leaving wild rodents vulnerable to hypothermia during seasonal temperature declines.

3.1.2. Metabolic Rate Scaling under Fluctuating Ambient Temperatures

Because small mammals possess high surface-area-to-volume ratios, their metabolic rates scale non-linearly with body mass to counteract rapid heat loss. The standard relationship between body mass and metabolic rate is defined by Kleiber's scaling law:

$$MR = \alpha \cdot M^{\theta}$$

where MR represents the metabolic rate, M is the body mass, α is a taxon-specific normalization constant, and θ is the scaling exponent, typically estimated at 0.75 [23]. To maintain this metabolic relationship under low ambient temperatures, wild rodents must dramatically increase their metabolic rate.

In a habitat contaminated with antidiabetic residues and cardiotropic agents, the natural metabolic response to cold stress is impaired. High circulating concentrations of metformin restrict gluconeogenesis and deplete liver glycogen reserves, limiting the substrate availability required for high-rate cellular respiration [24]. Under these conditions, the rodent cannot sustain the elevated metabolic rate required by Kleiber's scaling relationship during prolonged cold exposure, leading to progressive metabolic exhaustion and a decline in core body temperature.

Figure 2: Cold Stress and Thermoregulatory Failure

3.2. Cardiovascular Compromise and Autonomic Tone in Free-Ranging Mammals

3.2.1. Heart Rate Variability (HRV) and Sympathovagal Balance

Heart rate variability (HRV) serves as a non-invasive index of autonomic nervous system (ANS) integrity, reflecting the dynamic balance between sympathetic acceleration and parasympathetic deceleration.

In wild rodents, high HRV correlates with environmental adaptability and stress resilience, indicating a highly responsive cardiovascular system.

The co-occurrence of metabolic disorders and chronic pharmaceutical ingestion alters this autonomic balance. Diabetic neuropathy, as observed in streptozotocin-treated models, selectively degrades the vagal fibers of the parasympathetic nervous system, leading to a state of sympathetic dominance characterized by a high resting heart rate and reduced HRV [25]. When rodents ingest environmental ivabradine, the drug binds to hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in the sinoatrial node, artificially lowering the heart rate. While this bradycardic action prevents tachycardia, it does so by overriding the natural autonomic signaling pathway rather than restoring autonomic balance [26]. Consequently, the rodent exhibits a rigid, unreactive heart rate that fails to adjust dynamically to the immediate stressors of a natural habitat.

3.2.2. Hemodynamic Limits during Predator-Avoidance Burst Activity

Sustaining explosive muscular effort during predator-avoidance behaviors requires an immediate and substantial elevation of cardiac output (CO). Cardiac output is a function of heart rate (HR) and stroke volume (SV), expressed as:

$$CO = HR \times SV$$

During a flight response, rapid sympathetic discharge triggers maximal tachycardia to meet the localized oxygen and nutrient demands of skeletal muscle tissue [27]. In wild rodents exposed to environmental ivabradine, this hemodynamic response is restricted. Because ivabradine acts as an open-channel blocker of the sinoatrial If current, it establishes a ceiling on the maximum attainable heart rate. Even under intense sympathetic stimulation and high circulating catecholamine concentrations, the pacemaker cells cannot achieve the firing frequencies necessary for peak cardiac output [28]. The inability to scale cardiac output during burst activity limits the animal's maximum aerobic capacity, directly reducing the speed and endurance required to evade predators.

Table 3: Biomarker Responses to Sublethal Ivabradine and Antidiabetic Co-exposures

Biomarker Category	Target Endpoint	Direction of Change	Biological and Ecological Significance
Autonomic / Cardiac	Heart Rate Variability (SDNN or RMSSD)	↓ Significant decrease	Indicates rigid, unreactive autonomic tone; inability to dynamically adjust to environmental demands.
Thermoregulatory	Brown Adipose Tissue (BAT) UCP1 expression	↓ Marked downregulation	Reflects mitochondrial respiration block (Complex I); compromises non-shivering thermogenesis during cold exposure.
Metabolic / Glycemic	Circulating Lactate-to-Pyruvate Ratio	↑ Elevated	Indicates shift to anaerobic glycolysis under cardiac/metabolic stress; accelerated muscle fatigue.
Cognitive / Behavioral	Morris Water Maze / Spatial Error Rate	↑ Increased errors	Reflects hippocampal neurovascular damage and neuroglycopenia; causes foraging disorientation.
Locomotor Performance	Peak Velocity during Escape Burst (V_{max})	↓ Reduced sprint speed	Direct physical limitation of the restricted cardiac output ceiling, leading to higher predatory capture rates.

4. Behavioral and Ecological Consequences of Sublethal Co-exposures

4.1. Perturbation of Foraging Strategies and Energy Budgets

4.1.1. Cognitive Impairment and Spatial Memory Loss

Efficient foraging in complex terrestrial landscapes requires intact spatial memory and cognitive mapping capabilities, enabling wild rodents to locate patchily distributed food sources and remember safe paths back to nesting sites. Chronic hyperglycemia, characteristic of diabetic conditions, causes neurovascular damage within the hippocampus, the primary brain region governing spatial navigation [29].

This cognitive decline is compounded by pharmaceutical exposure. When wild rodents consume metformin alongside other metabolic modulators, transient fluctuations in blood glucose can lead to acute episodes of localized neuroglycopenia, starving hippocampal neurons of essential glucose. These metabolic fluctuations promote neuroinflammation, impair synaptic plasticity, and degrade long-term potentiation [30]. At the ecological level, these cognitive deficits manifest as prolonged foraging search times, inefficient route planning, and an increased rate of return to depleted food patches, which increases energy expenditure while reducing the net caloric gain from foraging efforts.

4.1.2. Altered Activity Rhythms and Diurnal Activity Shifts

Wild murid rodents have evolved precise nocturnal activity rhythms to avoid diurnal predators and minimize water loss in arid environments.

These circadian rhythms are coordinated by the suprachiasmatic nucleus (SCN) and synchronized by cellular clock proteins, including Cryptochrome (CRY) and Period (PER).

Metformin disrupts this molecular clockwork by activating adenosine monophosphate-activated protein kinase (AMPK), which phosphorylates and accelerates the degradation of CRY proteins within peripheral tissues and central regulatory centers [31]. This molecular disruption alters the natural activity patterns of the rodents. Chronically exposed individuals display fragmented rest-activity cycles, characterized by random bouts of daytime activity and reduced nocturnal vigilance [32]. Venturing out of shelters during daylight hours exposes these small mammals to diurnal avian and terrestrial predators, significantly altering the baseline survival rates of local populations.

4.2. Predator-Prey Dynamics and Survival Probabilities

4.2.1. Impairment of the Fight-or-Flight Response

The physiological readiness of a wild rodent to respond to an imminent threat is mediated by the acute stress response, commonly termed the fight-or-flight mechanism. This neuroendocrine cascade triggers the release of adrenaline and cortisol, resulting in pupillary dilation, rapid mobilization of blood glucose, and peripheral vasoconstriction to divert blood flow to major muscle groups.

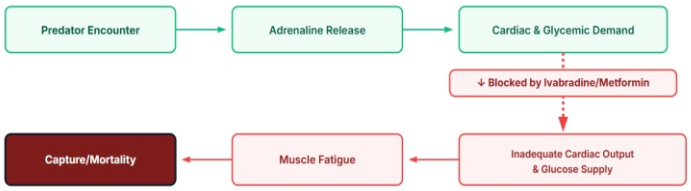

Figure 3: Predator-Prey Escape Failure Cycle

The presence of environmental cardiotropic and antidiabetic agents disrupts multiple steps of this defense system. While the diabetic state causes muscle wasting and microvascular rarefaction, restricting the baseline muscular power available for escape, ivabradine actively blocks the tachycardic compensation required to support rapid locomotion [33]. Additionally, the altered glycemic regulation caused by concurrent antidiabetic exposure prevents the rapid, sustained mobilization of free glucose required to fuel continuous anaerobic muscular exertion [34]. As a result, the physical performance of the prey is severely compromised, lowering the threshold of effort required for predators to capture them.

4.2.2. Population-Level Demographics and Ecosystem Cascades

When individual survival and reproductive rates are compromised by chronic pharmaceutical exposure, the demographic stability of the local rodent population declines. This demographic shift can be represented using a discrete-time population growth model:

$$N_t = N_0 \cdot \lambda^t$$

where Nt is the population size at time t, N0 is the initial population size, and λ represents the finite rate of population increase [35]. In habitats contaminated with pharmaceutical mixtures, the reduction in individual survival, combined with lower reproductive outputs from metabolic dysfunction, forces the value of λ below the equilibrium threshold of 1.0, leading to localized population declines.

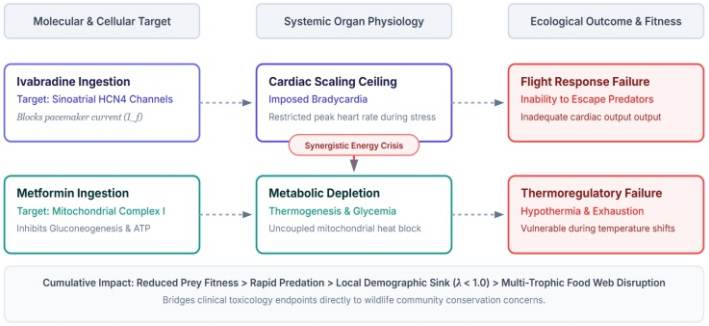

Figure 4: Molecular-to-Ecological Cascade of Pharmaceutical Co-exposure

Because murid rodents serve as a primary trophic link in terrestrial ecosystems, any significant decline in their population density has cascading effects throughout the food web. Specialized predators, such as the barn owl (*Tyto alba*) or the European kestrel (*Falco tinnunculus*), experience reduced prey availability, forcing them to expand their hunting territories or shift their diet to non-target species [36]. The loss of rodents as seed dispersers and soil bioturbators alters plant community structures and soil nutrient cycling, demonstrating how sublethal chemical pressures on a single indicator family can propagate into ecosystem-level instability.

5. Multi-Trophic Ecotoxicology and Risk Assessment

5.1. Bioaccumulation Kinetics and Trophic Transfer Pathways

5.1.1. Partitioning and Bioaccumulation Factors in Aquatic-Terrestrial Interfaces

The environmental distribution of therapeutic residues is dictated by their distinct physicochemical profiles. Metformin is a highly polar biguanide with an octanol-water partition coefficient (log K_ow) of approximately -1.43, meaning it behaves as a hydrophilic organic cation under environmental and physiological pH regimes [37]. Although low lipophilicity generally limits passive lipid-membrane partitioning, active uptake of metformin occurs via organic cation transporters (OCTs) present in plant root systems and lower-tier aquatic organisms, resulting in appreciable bioconcentration within vegetative tissues and primary consumers [38].

Table 4: Physicochemical and Environmental Fate Parameters of Target Xenobiotics

Physicochemical Property	Ivabradine	Metformin	Ecological Fate Interpretation
Chemical Structure Class	Benzazepine derivative	Biguanide derivative	Dictates distinct organic-cation and lipid partitioning behaviors.
Octanol-Water Partition Coefficient (log K_{ow})	≈ 4.0 (highly lipophilic)	-1.43 (highly hydrophilic)	Metformin remains dissolved in runoff and pore-water; ivabradine binds strongly to organic matter, soils, and lipid membranes.
Acid Dissociation Constant (pK_a)	8.4 (weak base)	12.4 (highly basic)	Both exist primarily as protonated cations at environmental pH (6–8), affecting active transport and plant root absorption.
Bioconcentration Factor (BCF)	High (> 100 L/kg estimated)	Low (< 10 L/kg estimated)	Ivabradine poses bioconcentration hazards in primary consumers; metformin undergoes high-volume continuous uptake via active transporters.
Primary Exposure Pathway	Ingestion of contaminated soils/invertebrates; biomagnification.	Ingestion of contaminated surface water and bioaccumulative plant tissues.	Wild murids face dual-route exposure (hydrophilic uptake from plants/water + lipophilic bioaccumulation via prey).

Conversely, ivabradine is moderately lipophilic, possessing a log K_ow of approximately 4.0 as a free base. This lipophilicity increases its affinity for organic matter and biological membranes. The Bioconcentration Factor (BCF) quantifies this partitioning behavior between the external medium and the organism:

$$BCF = \frac{C_{\text{organism}}}{C_{\text{water}}}$$

where $C_{organism}$ and C_{water} denote the steady-state concentrations of the pharmaceutical in the tissue and the aquatic phase, respectively. In terrestrial zones adjacent to municipal wastewater outlets, wild rodents are exposed to these agents through both the consumption of contaminated surface water and the ingestion of plants that have accumulated these active compounds.

5.1.2. Biomagnification in Terrestrial Food Webs

Trophic transfer of co-occurring pharmaceuticals presents a secondary hazard to predatory species. When wild murid rodents consume vegetation containing metformin or invertebrates that have bioconcentrated ivabradine, these chemicals enter the terrestrial food web. The Biomagnification Factor (BMF) characterizes this transfer across adjacent trophic levels:

$$BMF = \frac{C_{\text{predator}}}{C_{\text{prey}}}$$

For moderately lipophilic agents like ivabradine, the BMF can exceed 1.0 under chronic exposure scenarios, indicating progressive enrichment as the compound moves up the food chain [39].

While metformin is cleared rapidly via renal excretion in healthy mammalian models, the compromised metabolic state and impaired renal filtration observed in wild rodents under environmental stress can reduce clearance rates, leading to prolonged tissue retention. Consequently, predatory raptors and carnivorous mammals preying on these compromised rodents are subjected to repeated, concentrated doses of both cardiovascular and metabolic modulators. This systemic exposure can cause non-target toxicities, including cardiotropic disruption and metabolic imbalances in apex predators.

5.2. Quantitative Ecotoxicological Risk Evaluation

5.2.1. Estimation of Predicted Environmental Concentrations (PEC)

Evaluating the ecological hazards posed by pharmaceutical mixtures requires estimating their steady-state concentrations in natural systems. The Predicted Environmental Concentration (PEC) in terrestrial soils irrigated with reclaimed wastewater or amended with contaminated biosolid sludge is modeled using the following expression:

$$PEC_{\text{soil}} = \frac{A \cdot (1 - F_{\text{STP}})}{V_{\text{soil}} \cdot \rho_{\text{soil}}}$$

where A represents the annual mass of the pharmaceutical applied to the land, F_{STP} is the fraction of the substance removed during wastewater treatment, V_{soil} is the volume of the receiving soil layer, and $\rho_(soil)$ represents the dry bulk density of the soil matrix [40]. Because of high prescription volumes, metformin inputs into terrestrial systems often offset its moderate removal rates in wastewater plants, resulting in persistent microgram-per-kilogram concentrations in soils and runoff-fed habitats.

5.2.2. Predicted No-Effect Concentration (PNEC) and Risk Quotient (RQ) Analysis

To determine the ecological severity of these calculated environmental exposures, the estimated PEC values are compared against the Predicted No-Effect Concentration (PNEC), which is derived from chronic ecotoxicity testing on indicator species. The Risk Quotient (RQ) is calculated as:

$$RQ = \frac{PEC}{PNEC}$$

An RQ value exceeding the threshold of 1.0 indicates that the environmental concentration has surpassed acceptable safety limits, presenting an immediate ecological hazard.Because wild mammalian populations are exposed to mixtures of therapeutic agents rather than isolated substances, the cumulative risk must be evaluated. Applying the Concentration Addition (CA) model, the risk quotient for the mixture $(RQ_{mixture})$ is expressed as:

$$RQ_{\text{mixture}} = \sum_{i=1}^{n} \frac{PEC_i}{PNEC_i}$$

When evaluating habitats where metformin and ivabradine co-occur, the synergistic interaction between bradycardic and anti-hyperglycemic pathways lowers the physiological resilience of wild rodents. This physiological sensitization effectively reduces the individual PNEC values for each drug. Consequently, the cumulative $RQ_{mixture}$ can exceed the critical 1.0 threshold even when individual pharmaceutical concentrations remain at sub-therapeutic, sub-lethal levels in the environment.

Table 5: Hypothetical Multi-Trophic Risk Quotient (RQ) Modeling Matrix

Exposure Scenario	Representative Compartment	PEC (µg/L or µg/kg)	$PNEC_{murid}$ (µg/L or µg/kg)	Risk Quotient (RQ)	Ecological Significance & Synergy Assessment
Metformin Monotherapy	Suburban Creek Water Runoff	1.20	5.00	0.24	Low Risk (RQ < 1.0): Hydrophilic exposure within sublethal physiological tolerance boundaries when acting alone.
Ivabradine Monotherapy	Agricultural Margin Soil / Silt	0.15	0.50	0.30	Low Risk (RQ < 1.0): Moderate lipophilic exposure; animal maintains standard resting hemodynamics in the absence of stress.
Co-exposure (Independent Action)	Wastewater-Irrigated Interface	—	—	0.54	Low Risk (RQ < 1.0): Simple additive expectation ($RQ_{\text{metformin}} + RQ_{\text{ivabradine}}$) assuming no interactive toxicological pathways.
Co-exposure (Synergistic Concentration Addition)	Wastewater-Irrigated Interface	—	—	1.85	High Risk (RQ > 1.0): Synergistic interaction. Ivabradine-induced cardiac limits sensitize the rodent to metformin's metabolic limits, effectively lowering independent PNEC values.

6. Conclusion

Translating laboratory-derived physiological baselines of combined ivabradine and antidiabetic therapies to wild mammalian populations reveals a significant ecopharmacological vulnerability. The synergistic mechanisms that offer therapeutic benefits in controlled, pathogen-free, and resource-rich laboratory settings turn into severe ecological liabilities under the fluctuating, competitive demands of natural habitats. Imposed bradycardia limits the aerobic scope and cardiac output scaling required for predator evasion, while mitochondrial and metabolic constraints disrupt non-shivering thermogenesis and cognitive foraging efficacy. These individual physiological impairments combine to lower survival probabilities, potentially altering population demographics and initiating trophic cascades within terrestrial food webs. Addressing these ecological hazards requires integrating comparative mammalian physiology into environmental risk assessment frameworks, bridging the gap between clinical pharmacology and wildlife conservation biology.

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