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Recent Advances in Deploying d-Block Noble Metal Scaffolds for Marginalized Parasitic Maladies

Bhoomika Chaudhary[1], Piyush Chahal[2], Jaideep Kumar Singh Yadav[3], Supriya Singh[4], Mohd Junaid[5], Shivanshu Sharma[6], Akriti Singh[7], Mekhala[8*], Nidhi Bhati[91]

[1]Assistant Professor, Charak School of Pharmacy, Chaudhary Charan Singh University, Meerut, Uttar Pradesh, India.

[2]Associate Professor, School of Pharmacy, Lingaya's Vidyapeeth, Faridabad, Haryana 121002

[3]Tabish Pharmacy School, Angnakole, Sultanpur - 228118, India

[4]Assistant Professor, School of Pharmaceutical Sciences, Jaipur National University, Jagatpura, Jaipur, Rajasthan 302017

[5]Associate Professor, Department of Pharmacy, Mohammad Ali Jauhar University Rampur Uttar Pradesh India 244901. Email- pharmajunaid@gmail.com [6]School of Pharmacy, Sharda University, Plot No 32,34, Knowledge Park-III, Greater Noida, Uttar Pradesh, 201310[7]Assistant professor, School of Pharmacy, Lingayas Vidyapeeth Faridabad Nachauli, Jasana Road, Haryana 121002 India. Email-singhakriti1522@gmail.com, Orcid id 0009-0007-7301-762X [8]Department of Computer Science & Engineering, Sharda University, Greater Noida, India Email-gupta26mekhala@gmail.com [9]Vishveshwarya Group of Institutions, Ghaziabad-Bulandshahar G.T. Road, NH-91, Greater Noida Phase-II, Gautam Buddha Nagar, UP-201314Corresponding

Author Email: gupta26mekhala@gmail.com

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Abstract

Neglected tropical diseases and malaria continue to impose a substantial health burden on marginalized populations, while conventional antiparasitic therapies are increasingly limited by drug resistance, toxicity, poor pharmacokinetic profiles, and inadequate accessibility. This review highlights recent advances in the application of d-block noble-metal scaffolds, including ruthenium, iridium, gold, platinum, silver, and palladium complexes, as promising alternatives for the development of next-generation antiparasitic agents. Their variable oxidation states, tunable ligand-exchange kinetics, diverse three-dimensional geometries, redox activity, and ability to interact with parasite-specific biomolecular targets provide important advantages over conventional organic chemotypes. Noble-metal complexes can disrupt essential parasitic processes by inhibiting trypanothione reductase and thioredoxin reductase, inducing reactive oxygen species-mediated oxidative stress, impairing mitochondrial function, interfering with heme detoxification, and damaging DNA and other macromolecules. Hybrid metallodrugs incorporating nitroimidazole, quinoline, Schiff-base, phosphine, or N-heterocyclic carbene ligands may further achieve synergistic, multi-target activity and potentially reduce the development of resistance. The review also discusses structural architectures such as piano-stool, polypyridyl, cyclometalated, square-planar, and heterobimetallic complexes. Despite their considerable promise, clinical translation remains constrained by off-target toxicity, serum-protein binding, limited tissue penetration, rapid ligand exchange, and insufficient in vivo validation. Rational structure–activity relationship optimization, nano-delivery systems, density functional theory, and artificial intelligence-assisted screening may overcome these barriers.

Introduction

The unmet need in parasitic chemotherapy is epitomized by the staggering global burden of WHO-prioritized Neglected Tropical Diseases (NTDs) and malaria, which collectively afflict over 1.7 billion individuals annually, predominantly within marginalized populations residing in sub-Saharan Africa, South Asia, and Latin America, where poverty, inadequate sanitation, and limited healthcare access exacerbate transmission dynamics and sustain a cycle of morbidity and mortality that incurs approximately 14.1 million disability-adjusted life years (DALYs) and 119,000 deaths annually, with children under five and pregnant women bearing the disproportionate brunt of this epidemiological crisis (Yajima et al., 2023). This dire landscape is further compounded by the molecular failure mechanisms of legacy organic antiparasitic agents, including trivalent antimonials for leishmaniasis, benznidazole and nifurtimox for Chagas disease, and artemisinin derivatives for malaria, all of which are increasingly undermined by rapid resistance emergence driven by multifactorial genetic and biochemical adaptations such as the modulation of key enzymes required for pro-drug activation (e.g., nitroreductases like TcNTR in Trypanosoma cruzi), overexpression of ATP-binding cassette (ABC) transporters facilitating efflux-mediated drug clearance, upregulation of antioxidant defense systems including superoxide dismutase and trypanothione reductase to neutralize reactive oxygen species generated by nitro-heterocyclic compounds, and mutations in DNA repair pathways that confer survival advantages under chemotherapeutic pressure, thereby rendering these frontline regimens progressively obsolete in endemic regions with high transmission intensity (Fitzpatrick et al., 2018). Compounding these efficacy challenges is the high host cytotoxicity and severe side-effect profiles intrinsic to current antiparasitic pharmacotherapies, wherein trivalent antimonials induce cardiotoxicity, hepatotoxicity, and pancreatitis through mitochondrial dysfunction and oxidative stress; benznidazole and nifurtimox provoke dermatological hypersensitivity reactions, peripheral neuropathy, and gastrointestinal distress via nitro-radical-mediated cellular damage; and artemisinin combinations, while generally safer, still elicit delayed hemolysis and rare but serious anaphylactoid responses, collectively contributing to poor patient compliance, treatment discontinuation, and suboptimal therapeutic outcomes that perpetuate reservoir populations and facilitate recrudescence (Hotez et al., 2016). These limitations underscore an urgent demand for novel structural modalities capable of accessing unexploited biological targets within parasitic pathogens, such as invariant surface glycoproteins, kinetoplastid-specific metabolic enzymes (e.g., trypanothione synthetase, N-myristoyltransferase), apicoplast

biogenesis machinery in Plasmodium spp., and epigenetic regulators like histone deacetylases, which offer the potential for selective toxicity, reduced resistance liability, and improved pharmacokinetic-pharmacodynamic profiles that align with the therapeutic imperatives of safety, efficacy, and accessibility in resource-constrained settings (Martins-Melo et al., 2018). The convergence of these factors epidemiological urgency, mechanistic obsolescence of legacy drugs, intolerable toxicity burdens, and the paucity of innovative chemotypes necessitates a paradigm shift toward rational drug design leveraging fragment-based screening, structure-activity relationship (SAR) optimization, and target-based phenotypic assays to identify next-generation antiparasitics that transcend the limitations of current chemotherapy and fulfill the critical unmet medical need inherent in the global fight against parasitic diseases(Ochola et al., 2021).

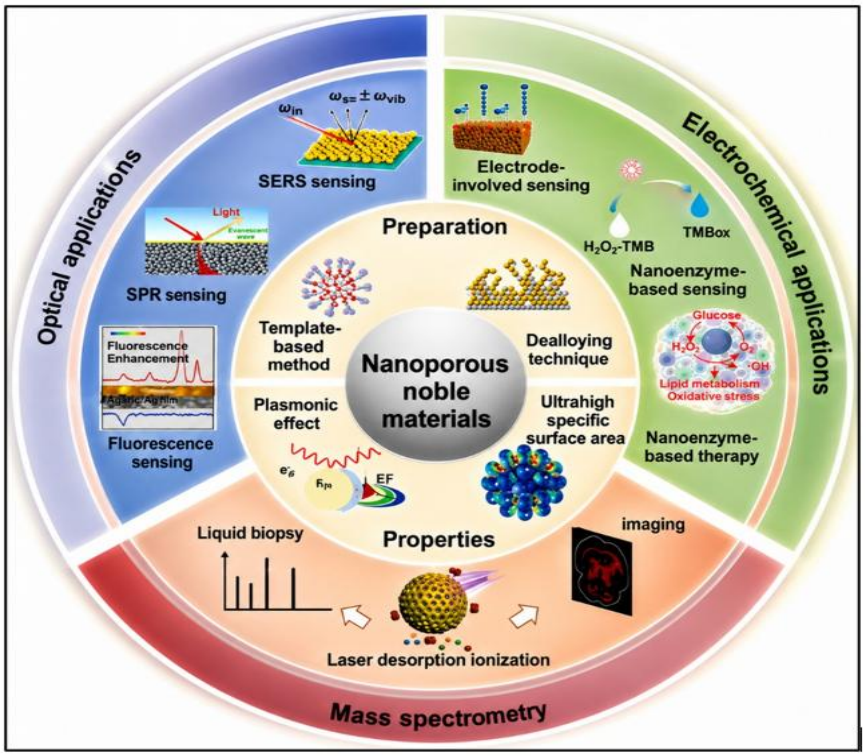


Figure 1: Overview of properties, synthesis strategies, and biomedical applications of porous noble metal-based nanomaterials.

The Metallodrug Paradigm Shift in Parasitology

The metallodrug paradigm shift in parasitology represents a strategic transition from purely organic scaffolds to d-block noble metal–based coordination complexes, leveraging the unique physicochemical attributes of ruthenium (Ru), iridium (Ir), gold (Au), platinum (Pt), silver (Ag), and palladium (Pd) to overcome limitations of conventional antiparasitic agents (Bangert et al., 2017). These transition metals confer variable oxidation states (e.g., Ru(II)/Ru(III),

Ir(III)/Ir(IV), Au(I)/Au(III), Pt(II)/Pt(IV)), enabling redox-responsive activation within the reductive microenvironments characteristic of parasitic infections, akin to bio-reductive prodrug strategies in oncology (Ackley et al., 2021). Their ligand exchange kinetics slower for square-planar Pt (II) and Au(I) complexes yet tunable via ancillary ligands in octahedral Ru (II) or Ir(III) species facilitate selective interactions with parasitic biomolecules such as thiol-rich enzymes (e.g., trypanothione reductase, thioredoxin reductase) while minimizing off-target host toxicity (Casulli et al., 2021). Distinct three-dimensional geometries, including octahedral, square-planar, and half-sandwich architectures, impart steric and electronic complementarity to parasitic protein pockets unattainable by planar organic pharmacophores, thereby enhancing target specificity and circumventing efflux-mediated resistance mechanisms (Rees et al., 2019; Bhati et al., 2025). Repurposing concepts from platinum-based oncology, such as cisplatin's DNA cross-linking and carboplatin's prodrug design, has inspired targeted antiparasitic coordination chemistry wherein Pt(IV) prodrugs conjugated to siderophores (e.g., deferoxamine) exploit microbial iron-uptake pathways for selective internalization, as demonstrated in Pt(IV)–DFO conjugates against Aspergillus and potentially adaptable to protozoan parasites (Montaner-Angoiti et al., 2023). Synergistic drug design strategies further integrate active organic antiparasitic pharmacophores such as nitroimidazoles, quinolines, or Schiff bases directly into noble metal coordination spheres, yielding hybrid metallodrugs that combine metal-centered redox catalysis with ligand-based enzyme inhibition (Maia et al., 2023). For instance, cyclometallated Pt(II) complexes bearing 2-phenylpyridine ligands exhibit selective antileishmanial activity via mitochondrial membrane disruption and reactive oxygen species (ROS) generation, while Au(I) auranofin derivatives irreversibly inhibit protozoan thioredoxin reductase through selenocysteine coordination, disrupting redox homeostasis essential for parasite survival (Wilson et al., 2020). Ruthenium polypyridyl complexes, meanwhile, demonstrate photoactivatable cytotoxicity against Trypanosoma cruzi, leveraging ligand-to-metal charge transfer (LMCT) for spatiotemporal control of drug action (Ventura-Garcia et al., 2013). Such rational design paradigms merging the metabolic stability, multi-target potential, and stimuli-responsiveness of noble metals with the proven efficacy of organic antiparasitics herald a new era of precision metallodrug therapeutics capable of addressing the urgent need for novel treatments against neglected tropical diseases (Okwor & Uzonna et al., 2016).

Table 1: Overview of Conventional Antiparasitic Drugs, Their Mechanisms, Resistance, and Major Limitations

Drug	First Use	Target/Disease	Simplified Mechanism	Resistance	References
Pentamidine	1937	*T. brucei* (early-stage HAT); cutaneous leishmaniasis	Interacts with parasite DNA and affects topoisomerase and mitochondrial function	Reduced uptake due to TbAT1/TbAQP2 alterations	(Grifferty et al., 2021)
Suramin	1920	Early-stage *T. b. rhodesiense* HAT	Disrupts ATP metabolism and inhibits glycolytic enzymes	Changes in uptake-related proteins and RuvBL1 mutations	(de Koning et al., 2020)
Melarsoprol	1949	Late-stage *T. b. rhodesiense* HAT	Disturbs redox balance by targeting trypanothione metabolism	AQP2 and TbAT1 transporter mutations	(Alcântara et al., 2018)
Eflornithine	1990	Second-stage *T. b. gambiense* HAT	Blocks ornithine decarboxylase and polyamine synthesis	TbAAT6 gene mutation or deletion	(Tauheed et al., 2025)
NECT	2009	Stage 2 *T. b. gambiense* HAT	Combines DNA damage with inhibition of polyamine synthesis	Reduced nitroreductase activity or impaired drug uptake	(Rees et al., 2019)

Fexinidazole	2018	Early and non-severe late-stage HAT	Activated metabolites cause damage to parasite DNA and proteins	Loss or reduced expression of nitroreductase	(Hotez et al., 2016)
Benznidazole	1972	*T. cruzi*	Generates reactive metabolites causing oxidative and DNA damage	TcNTR-1 mutations and genomic alterations	(Ackley et al., 2021)
Nifurtimox	1960	*T. cruzi*	Nitroreductive activation produces toxic oxidative stress	Mainly associated with altered nitroreductase activity	(Maia et al., 2023)
Miltefosine	2002	*Leishmania* spp.	Alters membrane lipid metabolism and mitochondrial function	Reduced uptake, increased efflux, and transporter mutations	(Grifferty et al., 2021)
Amphotericin B deoxycholate	1963	*Leishmania* spp.	Binds parasite ergosterol and forms membrane pores	Changes in membrane sterol composition	(Sunyoto et al., 2018)

Liposomal Amphotericin B	1997	*Leishmania* spp.	Targets ergosterol, causing membrane disruption	Altered sterol composition	(Das et al., 2021)

Structural Taxonomy of d-Block Noble Metal Scaffolds

The structural taxonomy of d-block noble metal scaffolds classifies organometallic and coordination architectures by metal oxidation state, ligand topology, and electronic configuration, enabling rational design of bioactive metallodrugs with predictable reactivity and pharmacokinetics (Miaka et al., 2025).

Ru(II/III) and Ir(III) Organometallics

Half-Sandwich "Piano-Stool" Complexes

Ru(II/III) and Ir(III) organometallics prominently feature half-sandwich "piano-stool" geometries, wherein a polyhapto aromatic ligand typically η^6-arene (e.g., benzene, p-cymene) for Ru or η^5-pentamethylcyclopentadienyl (Cp^*) for Ir occupies the facial coordination site as the "seat," while three monodentate or one bidentate plus one monodentate ligands form the "legs." This pseudooctahedral d^6low-spin configuration confers kinetic inertness yet allows ligand substitution at the apical site, crucial for bioconjugation and activation (Miaka et al., 2025lBhatt, Kumar, Kumar, et al., 2025). The hydrophobic face of the η^6-arene or Cp^*moiety enhances membrane permeability and promotes noncovalent interactions with biomacromolecules via π-stacking and van der Waals forces, as evidenced by increased cytotoxicity with higher arene hydrophobicity (Hodo & Hamer, 2017).

Polypyridyl and Photoredox-Active Architectures

Beyond piano-stool motifs, Ru(II) polypyridyl complexes (e.g., $[Ru(bpy)_3]^{2+}$derivatives) and Ir(III) cyclometalated species serve as photoredox-active scaffolds engineered for light-activated photodynamic antiparasitic therapy (PACT) (Segura et al., 2023). These architectures exhibit long-lived triplet excited states that facilitate energy or electron transfer to molecular oxygen, generating cytotoxic reactive oxygen species (ROS) such as singlet oxygen (Bhatt, Kumar, Singh, et al., 2025). Strategic ligand functionalization with extended π-systems or electron-donating/withdrawing groups tunes absorption maxima into the therapeutic window (600–800 nm), optimizing tissue penetration and selectivity for parasitic pathogens like *Leishmania* and *Trypanosoma* (Oranjin et al., 2025).

Au(I/III) and Pt(II)/Pd(II) Coordination Complexes Gold(I/III) Phosphine and NHC Complexes

Au(I) linear (d^{10}) and Au(III) square-planar (d^8) complexes bearing phosphine (e.g., PPh_3, dppm) or N-heterocyclic carbene (NHC) ligands display high thiol reactivity, targeting cysteine-rich

enzymes such as thioredoxin reductase (TrxR) and glutathione peroxidase (Giordani et al., 2016). The soft Au(I) center undergoes facile ligand exchange with biological thiols (e.g., glutathione), inducing redox imbalance and apoptosis, while Au(III) NHC scaffolds offer enhanced stability against reduction in physiological media (Garlapati et al., 2021;Bhatt, Singh, Garg, et al., 2025).

Table 2: Therapeutic Compounds and Emerging Strategies for Managing Oxidative Stress in Major Diseases

Disease Category	Drug/Compound	Key Action	Application	References
Neurodegenerative	Coenzyme Q10	Limits oxidative and inflammatory damage	Multiple sclerosis	(Giordani et al., 2016)
	N-acetylcysteine	Boosts glutathione-mediated antioxidant defense	Parkinson's disease	(Das et al., 2021)
	AGEs/RAGE inhibitors	Blocks oxidative and NF-κB-mediated inflammation	Alzheimer's disease	(Rees et al., 2019)
Cardiovascular	N-acetylcysteine	Restores antioxidant capacity and lowers ROS	CAD, myocardial infarction	(Sunyoto et al., 2018)
	Quercetin/Resveratrol	Protects endothelium	Atherosclerosis	(Wilson et al., 2020)

		through antioxidant activity		
	MitoTEMPO	Reduces mitochondrial ROS	Heart failure, cardiac hypertrophy	(Das et al., 2021)
	SS-31	Improves mitochondrial function and limits ischemic injury	Myocardial ischemia, heart failure	(Ochola et al., 2021)
Cancer	Coenzyme Q10	Reduces oxidative stress and inflammation	Liver cancer adjunct therapy	(Yajima et al., 2023)
	Quercetin/Resveratrol	Provides antioxidant support in anticancer treatment	Various cancers	(Casulli et al., 2021)
	Doxorubicin	Promotes ROS-mediated tumor cell death	Metastatic breast cancer	(Alcântara et al., 2018)
Metabolic	N-acetylcysteine	Supports antioxidant defense and wound repair	Diabetic complications	(Ochola et al., 2021)
	Resveratrol	Regulates AMPK signaling and improves	Type 2 diabetes	(Tauheed et al., 2025)

		vascular function		
	SGLT2 inhibitors	Activates AMPK and alleviates oxidative stress	Diabetes-related cardiovascular complications	(Rees et al., 2019)
Emerging approaches	Mitochondrial adaptive regulation	Enhances mitochondrial adaptation to stress	Metabolic vascular damage	(Sunyoto et al., 2018)
	Nrf2 activation	Induces endogenous antioxidant gene expression	Metabolic disorders	(Wilson et al., 2020)

Square-Planar Pt(II)/Pd(II) Scaffolds

Pt(II) and Pd(II) coordination complexes adopt square-planar geometries, classically exemplified by cisplatin, but modern variants incorporate non-innocent multidentate bio-ligands (e.g., terpyridines, porphyrins, Schiff bases) that participate in redox chemistry or exhibit intrinsic bioactivity (Bhatt, Patil, Ranjana, Soni, & Bagal, 2025). These ligands modulate electronic density at the metal center, influencing DNA binding affinity, cellular uptake, and resistance profiles. Pd(II) analogues often display faster ligand exchange kinetics than Pt(II), enabling rapid covalent adduct formation with nucleobases(Chugh, Dwivedi, Garg, Bhatt, & Gupta, 2025).

Heterobimetallic Constructs

Heterobimetallic scaffolds, such as ferrocene-Au or Ru-Au hybrids, integrate distinct pharmacophores to achieve dual-action mechanisms: redox-active ferrocene moieties generate ROS via Fenton-like cycles, while Au centers inhibit thiol-dependent enzymes (Bertram et al., 2024). Such synergistic architectures overcome multidrug resistance by simultaneously targeting multiple cellular pathways, exemplified by Ru(II)-arene-Au(I)-phosphine conjugates exhibiting sub-micromolar IC_{50} values against resistant cancer cell lines (Hong et al., 2020).

Mechanistic Pathways & Subcellular Targets

The antiparasitic efficacy of several phytochemicals and synthetic agents arises from their capacity to perturb redox homeostasis and disrupt essential metabolic circuits within protozoan pathogens (Tomar et al., 2026). These mechanisms converge on subcellular targets that

are either absent or structurally divergent in the mammalian host, thereby conferring selective toxicity (Khan et al., 2025).

Redox Cascade Disruption Catalytic Inhibition of Trypanothione Reductase (TR) and Thioredoxin Reductase (TrxR)

Trypanothione reductase (TR) and thioredoxin reductase (TrxR) are flavoenzymes central to the thioredoxin (Trx), a critical electron donor for ribonucleotide reductase and peroxiredoxins (Singh et al., 2026). Inhibition of these enzymes impairs the regeneration of reduced thiol pools, leading to the accumulation of oxidized protein thiols and the collapse of antioxidant defenses (Antinori et al., 2017). Structural studies reveal that active-site residues in parasitic TR and TrxR exhibit distinct conformations compared to their mammalian homologs (e.g., glutathione reductase), enabling selective inhibition by electrophilic compounds, metal chelators, or quinone-based agents (Sheikh et al., 2023).

Induction of Lethal Oxidative Stress via ROS Bursts

The blockade of TR and TrxR precipitates a catastrophic rise in intracellular reactive oxygen species (ROS), including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (- OH) (Sadhu et al., 2026). Under physiological conditions, ROS are neutralized by enzymatic antioxidants (e.g., superoxide dismutase, catalase, peroxiredoxins) and low-molecular-weight thiols (e.g., trypanothione, glutathione) (Basselin et al., 1996). However, when redox buffering capacity is compromised, ROS accumulate and initiate lipid peroxidation, maintenance of intracellular redox equilibrium in trypanosomatids and Plasmodium species, respectively (Meisner et al., 2023). TR catalyzes the NADPH-dependent reduction of trypanothione [$T(SH)_2$], a bis-glutathionylspermidine conjugate unique to kinetoplastid parasites, while TrxR reduces oxidized

protein carbonylation, and DNA strand breaks. In Plasmodium-infected erythrocytes, ROS bursts also promote heme-mediated oxidative damage, further exacerbating parasitic stress (Vercesi et al., 1992). The resultant oxidative milieu triggers mitochondrial dysfunction, activation of stress kinases (e.g., p38 MAPK), and ultimately apoptotic-like cell death in the parasite (Croft & Brazil, 1982).

Metabolic Blockade and Organelle Dysfunction

Inhibition of Hemobiotic Pathways and Prevention of β-Hematin Crystallization

In Plasmodium species, the detoxification of free heme released during hemoglobin catabolism is mediated by its biocrystallization into inert β-hematin (hemozoin) (Basselin et al., 2002). This process occurs within the acidic food vacuole and is catalyzed by histidine-rich proteins and lipid interfaces(Dwivedi, K., Garg, P., Chugh, B., Bhatt, P., & Kumar, A. 2025). Antimalarial agents such as chloroquine and certain phytochemicals (e.g., quinine derivatives, flavonoids) intercalate into growing heme crystals or bind free heme, thereby inhibiting β-hematin formation(Dwivedi, Garg, Chugh, Bhatt, & Kumar, 2025). The accumulation of cytotoxic

free heme induces membrane damage, ROS generation, and proteotoxic stress, culminating in parasite death (De Koning et al., 2001).

Selective Mitochondrial Accumulation and Bioenergetic Collapse

Certain lipophilic cations and amphiphilic compounds exhibit preferential accumulation in parasitic mitochondria due to the highly negative mitochondrial membrane potential ($\Delta\Psi_m$). Once internalized, these agents disrupt electron transport chain (ETC) complexes, uncouple oxidative phosphorylation, or induce mitochondrial permeability transition pore (mPTP) opening (Munday et al., 2014). The loss of $\Delta\Psi_m$ impairs ATP synthase activity, leading to rapid depletion of intracellular ATP pools(Fatima, Noor, Bhatt, Sethi, & Gupta, 2026). In Trypanosoma and Leishmania, which rely heavily on mitochondrial respiration during specific life-cycle stages, this bioenergetic crisis is lethal (Davidson et al., 2009). Additionally, mitochondrial ROS production is amplified under these conditions, creating a feed-forward loop of oxidative damage and organelle failure (Shalev-Benami et al., 2017).

Translational Bottlenecks and Future Perspectives

Translating promising in vitro anticancer and antiparasitic nanotherapeutics into clinically viable treatments is impeded by pharmacokinetic liabilities, off-target toxicity, and inadequate tissue penetration (Maarouf et al., 1997). Addressing these bottlenecks requires rational modulation of molecular descriptors, strategic engineering of nano-delivery platforms, and integration of machine learning (ML) and quantum-chemical modeling to accelerate structure–activity relationship (SAR) optimization (Kimutai et al., 2017).

Toxicity Modulation and SAR Optimization

Fine-tuning of Lipophilicity (log P) and Ligand Labilization Rates

The Selectivity Index (SI = CC50/IC50) is a critical pharmacodynamic metric that quantifies the therapeutic window between cytotoxicity to host cells (CC50) and efficacy against target pathogens or tumor cells (Sundar et al., 2019). Optimal log P values (typically 2–4 for small-molecule drugs) enhance membrane permeability while minimizing nonspecific accumulation in lipid-rich off-target tissues (Heidari-Kharaji et al., 2025). Excessive lipophilicity (log P > 5) promotes sequestration in adipose depots and hepatic metabolism via cytochrome P450 enzymes, reducing systemic exposure and elevating toxicity risks (Kamiński et al., 2014). Conversely, overly hydrophilic compounds (log P < 1) exhibit poor cellular uptake and rapid renal clearance. Ligand labilization rates, the kinetics of metal–ligand dissociation in coordination complexes, must be tuned to ensure controlled release of active moieties within target cells while maintaining stability in circulation (Readio et al., 1982). Fast labilization leads to premature drug release and off-target effects, whereas slow dissociation limits intracellular bioavailability. SAR-driven iterative modification of donor atoms (e.g., N, O, S), chelate ring size, and steric bulk around the metal center enables precise control over dissociation constants (Kd) and half-

lives (t1/2) (Gruszecki et al., 2002). For instance, substituting labile aqua ligands with kinetically inert N-donor heterocycles in ruthenium or platinum complexes reduces off-target reactivity with serum proteins while preserving redox activation within hypoxic tumor microenvironments (Kumari et al., 2022).

Mitigating Off-Target Serum Protein Binding

Human serum albumin (HSA), the most abundant plasma protein, binds diverse xenobiotics via hydrophobic pockets (Sudlow sites I and II) and electrostatic interactions, significantly influencing drug distribution, metabolism, and bioavailability (Mondal et al., 2014). High-affinity HSA binding (>90%) prolongs circulation half-life but restricts free drug fractions available for tissue penetration, thereby diminishing therapeutic efficacy. Moreover, HSA-bound drugs may undergo albumin-mediated endocytosis in non-target cells (e.g., hepatocytes via ASGPR), exacerbating toxicity (Wijnant et al., 2022). Strategies to mitigate off-target HSA binding include: (i) introducing polar or ionizable groups to reduce hydrophobic interactions; (ii) employing prodrug approaches that mask HSA-binding motifs until enzymatic activation at target sites; and (iii) designing nano-carriers (e.g., PEGylated liposomes, polymeric micelles) that sterically shield drug payloads from protein adsorption (Frézard et al., 2023). Notably, albumin-based nanoparticles (e.g., Abraxane) exploit HSA's natural transport pathways (e.g., gp60/SPARC-mediated transcytosis) for tumor-selective delivery while minimizing off-target binding through surface functionalization with targeting ligands (Cirri et al., 2022).

4.2 Nano-Delivery Platforms and Machine Learning Integration

Targeted Encapsulations for Tissue Barrier Penetration

Advanced nano-delivery platforms, such as metal–organic frameworks (MOFs) and lipid nanoparticles (LNPs), offer tunable porosity, high drug-loading capacity, and surface functionalization capabilities to overcome biological barriers (Chiaverini et al., 2025). For African Trypanosomiasis (sleeping sickness), where parasites invade the central nervous system (CNS), crossing the blood–brain barrier (BBB) is paramount (Cirri et al., 2021). LNPs engineered with ionizable lipids and brain-targeting ligands (e.g., transferrin, angiopep-2) facilitate receptor-mediated transcytosis across BBB endothelial cells. Intranasal administration of mRNA-loaded LNPs further bypasses the BBB via olfactory/trigeminal pathways, enabling direct CNS delivery with minimal peripheral exposure (Ma et al., 2025). MOFs, with their crystalline porous structures, allow precise encapsulation of antiparasitic agents (e.g., suramin, melarsoprol) and controlled release via pH- or enzyme-responsive linkers. Surface modification with polyethylene glycol (PEG) or zwitterionic polymers reduces opsonization and extends circulation time, enhancing accumulation in infected tissues (Smith et al., 2018).

Computational DFT and AI-Guided Screening

Density functional theory (DFT) provides

quantum-mechanical insights into metal–ligand bonding energies, redox potentials, and electronic structures, enabling prediction of complex stability and reactivity (Li et al., 2016). Coupled with ML algorithms trained on large datasets of physicochemical descriptors (log P, pKa, molecular weight) and biological endpoints (IC50, CC50), AI-guided screening accelerates the identification of candidates with optimal parasitic selectivity and minimal host toxicity (Deben et al., 2024). For example, graph neural networks (GNNs) can predict BBB permeability scores based on molecular fingerprints, prioritizing compounds for experimental validation (Wang et al., 2024). Integration of DFT-calculated binding affinities with ML models further refines SAR landscapes, guiding the design of next-generation nanotherapeutics with enhanced translational potential (Pushpakom et al., 2018).

Conclusion

D-block noble-metal scaffolds have emerged as promising platforms for addressing the limitations of conventional antiparasitic chemotherapy. Ruthenium, iridium, gold, platinum, palladium, and related metal complexes possess distinctive redox properties, coordination geometries, ligand-exchange kinetics, and electronic characteristics that enable interactions with parasite-specific molecular targets. Their antiparasitic activity may involve simultaneous disruption of thiol-dependent redox systems, inhibition of trypanothione reductase and thioredoxin reductase, excessive reactive oxygen species generation, mitochondrial dysfunction, DNA damage, membrane destabilization, and interference with heme detoxification pathways. Such multi-target mechanisms are particularly valuable for overcoming drug resistance associated with altered drug uptake, enhanced efflux, nitroreductase modification, antioxidant-system activation, and changes in membrane composition. Hybrid complexes containing biologically active ligands, including quinolines, nitroimidazoles, Schiff bases, phosphines, and N-heterocyclic carbenes, may further improve selectivity and therapeutic performance through synergistic metal- and ligand-mediated actions. Nevertheless, the clinical development of these agents remains constrained by host toxicity, limited selectivity, serum-protein binding, uncertain metabolic stability, poor tissue penetration, and insufficient pharmacokinetic and in vivo safety data. Future research should therefore emphasize systematic structure–activity relationship studies, optimization of lipophilicity and ligand-labilization rates, parasite-targeted nano-delivery, and evaluation against resistant strains and clinically relevant parasite stages. Integration of density functional theory, molecular modelling, and machine-learning-assisted screening can accelerate the identification of stable, selective, and bioavailable candidates.

References

1. Yajima, A., Lin, Z., Mohamed, A. J., Dash, A. P., & Rijal, S. (2023). Finishing the task of eliminating neglected tropical diseases (NTDs)

in WHO South-East Asia region: Promises kept, challenges, and the way forward. The Lancet Regional Health – Southeast Asia, 18, 100302. https://doi.org/10.1016/j.lansea.2023.100302

2. Fitzpatrick, C., Bangert, M., Mbabazi, P. S., Mikhailov, A., Zouré, H., Polo Rebollo, M., et al. (2018). Monitoring equity in universal health coverage with essential services for neglected tropical diseases: An analysis of data reported for five diseases in 123 countries over 9 years. The Lancet Global Health, 6, e980–e988. https://doi.org/10.1016/S2214-109X(18)30307-3

3. Hotez, P. J., Pecoul, B., Rijal, S., Boehme, C., Aksoy, S., Malecela, M., et al. (2016). Eliminating the neglected tropical diseases: Translational science and new technologies. PLoS Neglected Tropical Diseases, 10, e0003895. https://doi.org/10.1371/journal.pntd.0003895

4. Martins-Melo, F. R., Carneiro, M., Ramos, A. N., Jr., Heukelbach, J., Ribeiro, A. L. P., & Werneck, G. L. (2018). The burden of neglected tropical diseases in Brazil, 1990–2016: A subnational analysis from the Global Burden of Disease Study 2016. PLoS Neglected Tropical Diseases, 12, e0006559. https://doi.org/10.1371/journal.pntd.0006559

5. Ochola, E. A., Karanja, D. M. S., & Elliott, S. J. (2021). The impact of neglected tropical diseases (NTDs) on health and wellbeing in sub-Saharan Africa (SSA): A case study of Kenya. PLoS Neglected Tropical Diseases, 15, e0009131. https://doi.org/10.1371/journal.pntd.0009131

6. Bangert, M., Molyneux, D. H., Lindsay, S. W., Fitzpatrick, C., & Engels, D. (2017). The cross-cutting contribution of the end of neglected tropical diseases to the Sustainable Development Goals. Infectious Diseases of Poverty, 6, 73. https://doi.org/10.1186/s40249-017-0288-0

7. Ackley, C., Elsheikh, M., & Zaman, S. (2021). Scoping review of neglected tropical disease interventions and health promotion: A framework for successful NTD interventions as evidenced by the literature. PLoS Neglected Tropical Diseases, 15, e0009278. https://doi.org/10.1371/journal.pntd.0009278

8. Casulli, A. (2021). New global targets for NTDs in the WHO roadmap 2021–2030. PLoS Neglected Tropical Diseases, 15, e0009373. https://doi.org/10.1371/journal.pntd.0009373

9. Rees, C. A., Hotez, P. J., Monuteaux, M. C., Niescierenko, M., & Bourgeois, F. T. (2019). Neglected tropical diseases in children: An assessment of gaps in research prioritization. PLoS Neglected Tropical Diseases, 13, e0007111. https://doi.org/10.1371/journal.pntd.0007111

10. Montaner-Angoiti, E., & Llobat, L. (2023). Is leishmaniasis the new emerging zoonosis in the world? Veterinary Research Communications, 47, 1777–1799. https://doi.org/10.1007/s11259-023-10171-5

11. Maia, C., Conceição, C., Pereira, A., Rocha, R., Ortuño, M., Muñozid, C., Jumakanova, Z., Pérez-Cutillas, P., Özbel, Y., Töz, S., et al. (2023). The estimated distribution of autochthonous leishmaniasis by Leishmania infantum in Europe in 2005–2020. PLoS Neglected Tropical Diseases, 17, e0011497.

https://doi.org/10.1371/journal.pntd.0011497

12. Wilson, A. L., Courtenay, O., Kelly-Hope, L. A., Scott, T. W., Takken, W., Torr, S. J., & Lindsay, S. W. (2020). The importance of vector control for the control and elimination of vector-borne diseases. PLoS Neglected Tropical Diseases, 14, e0007831. https://doi.org/10.1371/journal.pntd.0007831

13. Ventura-Garcia, L., Roura, M., Pell, C., Posada, E., Gascón, J., Aldasoro, E., Muñoz, J., & Pool, R. (2013). Socio-cultural aspects of Chagas disease: A systematic review of qualitative research. PLoS Neglected Tropical Diseases, 7, e2410. https://doi.org/10.1371/journal.pntd.0002410

14. Okwor, I., & Uzonna, J. (2016). Social and economic burden of human leishmaniasis. The American Journal of Tropical Medicine and Hygiene, 94, 489. https://doi.org/10.4269/ajtmh.15-0408

15. Grifferty, G., Shirley, H., McGloin, J., Kahn, J., Orriols, A., & Wamai, R. (2021). Vulnerabilities to and the socioeconomic and psychosocial impacts of the leishmaniases: A review. Research and Reports in Tropical Medicine, 12, 135–151. https://doi.org/10.2147/RRTM.S278138

16. World Health Organization. (2025). Chagas disease (also known as American trypanosomiasis). https://www.who.int/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis)

17. de Koning, H. P. (2020). The drugs of sleeping sickness: Their mechanisms of action and resistance, and a brief history. Tropical Medicine and Infectious Disease, 5, 14. https://doi.org/10.3390/tropicalmed5010014

18. Alcântara, L. M., Ferreira, T. C. S., Gadelha, F. R., & Miguel, D. C. (2018). Challenges in drug discovery targeting TriTryp diseases with an emphasis on leishmaniasis. International Journal for Parasitology: Drugs and Drug Resistance, 8, 430–439. https://doi.org/10.1016/j.ijpddr.2018.09.006

19. Tauheed, A. M., Danazumi, A. U., Adepoju, O. A., Kobo, P. I., Adamu, A., & Balogun, E. O. (2025). Kinetoplastid diseases: Insights into the mechanisms of drug action and resistance for novel drug discovery. Aspects of Molecular Medicine, 5, 100071. https://doi.org/10.1016/j.amolm.2025.100071

20. Sunyoto, T., Potet, J., & Boelaert, M. (2018). Why miltefosine—A life-saving drug for leishmaniasis—is unavailable to people who need it the most. BMJ Global Health, 3, e000709. https://doi.org/10.1136/bmjgh-2018-000709

21. Das, A. M., Chitnis, N., Burri, C., Paris, D. H., Patel, S., Spencer, S. E. F., Miaka, E. M., & Castaño, M. S. (2021). Modelling the impact of fexinidazole use on human African trypanosomiasis (HAT) transmission in the Democratic Republic of the Congo. PLoS Neglected Tropical Diseases, 15, e0009992. https://doi.org/10.1371/journal.pntd.0009992

22. Miaka, E. M., Pasi, C. P., & Hasker, E. (2025). Fexinidazole for human African trypanosomiasis: The challenge of accessibility. The Lancet Global Health, 13, e789–e790. https://doi.org/10.1016/S2214-109X(25)00068-3

23. Gómez-Bravo, A., Cirignoli, S.,

Wehrendt, D., Schijman, A., León, C. M., Flores-Chaves, M., Nieto, J., Kieran, T. J., Abril, M., & Guhl, F. (2024). Zoonotic cycle of American trypanosomiasis in an endemic region of the Argentine Chaco, factors that influenced a paradigm shift. Insects, 15, 471. https://doi.org/10.3390/insects15070471

24. Hodo, C. L., & Hamer, S. A. (2017). Toward an ecological framework for assessing reservoirs of vector-borne pathogens: Wildlife reservoirs of Trypanosoma cruzi across the southern United States. ILAR Journal, 58, 379–392. https://doi.org/10.1093/ilar/ilx020

25. Segura, G. B. R., Ochoa, W. H. S., da Matta, V. L. R., Martínez, M., Tercero, C. R., Gonzalez, R. R., Pacheco, C. M. S., Flores, G. V. A., Silveira, F. T., Henriquez, M. M. R., et al. (2023). Can domestic dogs be considered a good reservoir of Leishmania (L.) infantum chagasi in an endemic area of nonulcerated cutaneous leishmaniasis in southern Honduras? Revista do Instituto de Medicina Tropical de São Paulo, 65, e24. https://doi.org/10.1590/S1678-9946202365024

26. Oranjin, S. V., Kami, H. G., Tohidi, F., & Mohammadi, Z. (2025). Ecological habitat of small mammals as reservoirs of Leishmania spp. in the endemic foci of cutaneous leishmaniasis, the North Iran. Journal of Zoonotic Diseases, 9, 717–729. https://doi.org/10.22034/jzd.2024.18522

27. Giordani, F., Morrison, L. J., Rowan, T. G., De Koning, H. P., & Barrett, M. P. (2016). The animal trypanosomiases and their chemotherapy: A review. Parasitology, 143, 1862–1889. https://doi.org/10.1017/S0031182016001268

28. Garlapati, R., Iniguez, E., Serafim, T. D., Mishra, P. K., Rooj, B., Sinha, B., Valenzuela, J. G., Srikantiah, S., Bern, C., & Kamhawi, S. (2021). Towards a sustainable vector-control strategy in the post kala-azar elimination era. Frontiers in Cellular and Infection Microbiology, 11, 641632. https://doi.org/10.3389/fcimb.2021.641632

29. Bertram, M. G., Costi, M. P., Thoré, E. S., Sabo-Attwood, T., & Brooks, B. W. (2024). One Health. Current Biology, 34, R517–R519. https://doi.org/10.1016/j.cub.2024.04.025

30. Hong, A., Zampieri, R. A., Shaw, J. J., Floeter-Winter, L. M., & Laranjeira-Silva, M. F. (2020). One Health approach to leishmaniases: Understanding the disease dynamics through diagnostic tools. Pathogens, 9, 809. https://doi.org/10.3390/pathogens9100809

31. Khan, Y., Lin, I.-C., Khan, S., Kanwal, M., Wajid, A., Khan, A., Noor, F., Almajwal, A. M., Chen, C.-C., & Qadeer, A. (2025). Knowledge, attitudes, and practices toward leishmaniasis and One Health: A cross-sectional study among medical and veterinary professionals. Frontiers in Veterinary Science, 11, 1515370. https://doi.org/10.3389/fvets.2024.1515370

32. Meisner, J., Kato, A., Lemerani, M. M., Miaka, E. M., Ismail, A. T., Wakefield, J., Rowhani-Rahbar, A., Pigott, D., Mayer, J. D., Lorton, C., et al. (2023). Does a One Health approach to human African trypanosomiasis control hasten elimination? A stochastic

compartmental modeling approach. Acta Tropica, 240, 106804. https://doi.org/10.1016/j.actatropica.2022.106804

33. Antinori, S., Galimberti, L., Bianco, R., Grande, R., Galli, M., & Corbellino, M. (2017). Chagas disease in Europe: A review for the internist in the globalized world. European Journal of Internal Medicine, 43, 6–15. https://doi.org/10.1016/j.ejim.2017.05.001

34. Sheikh, S. Y., Ansari, W. A., Hassan, F., Faruqui, T., Khan, M. F., Akhter, Y., Khan, A. R., Siddiqui, M. A., Al-Khedhairy, A. A., & Nasibullah, M. (2023). Drug repositioning to discover novel ornithine decarboxylase inhibitors against visceral leishmaniasis. Journal of Molecular Recognition, 36, e3021. https://doi.org/10.1002/jmr.3021

35. Basselin, M., Lawrence, F., & Robert-Gero, M. (1996). Pentamidine uptake in Leishmania donovani and Leishmania amazonensis promastigotes and axenic amastigotes. Biochemical Journal, 315, 631–634. https://doi.org/10.1042/bj3150631

36. Vercesi, A. E., & Docampo, R. (1992). Ca^{2+} transport by digitonin-permeabilized Leishmania donovani: Effects of Ca^{2+}, pentamidine and WR-6026 on mitochondrial membrane potential in situ. Biochemical Journal, 284, 463–467. https://doi.org/10.1042/bj2840463

37. Croft, S. L., & Brazil, R. P. (1982). Effect of pentamidine isethionate on the ultrastructure and morphology of Leishmania mexicana amazonensis in vitro. Annals of Tropical Medicine & Parasitology, 76, 37–43. https://doi.org/10.1080/00034983.1982.11687502

38. Basselin, M., Denise, H., Coombs, G. H., & Barrett, M. P. (2002). Resistance to pentamidine in Leishmania mexicana involves exclusion of the drug from the mitochondrion. Antimicrobial Agents and Chemotherapy, 46, 3731–3738. https://doi.org/10.1128/AAC.46.12.3731-3738.2002

39. De Koning, H. P. (2001). Uptake of pentamidine in Trypanosoma brucei brucei is mediated by three distinct transporters: Implications for cross-resistance with arsenicals. Molecular Pharmacology, 59, 586–592. https://doi.org/10.1016/S0026-895X(24)12250-X

40. Munday, J. C., Eze, A. A., Baker, N., Glover, L., Clucas, C., Andrés, D. A., Natto, M. J., Teka, I. A., McDonald, J., Lee, R. S., et al. (2014). Trypanosoma brucei aquaglyceroporin 2 is a high-affinity transporter for pentamidine and melaminophenyl arsenic drugs and the main genetic determinant of resistance to these drugs. Journal of Antimicrobial Chemotherapy, 69, 651–663. https://doi.org/10.1093/jac/dkt442

41. Davidson, R. N., den Boer, M., & Ritmeijer, K. (2009). Paromomycin. Transactions of the Royal Society of Tropical Medicine and Hygiene, 103, 653–660. https://doi.org/10.1016/j.trstmh.2008.09.008

42. Webster, C. M., & Shepherd, M. (2023). A mini-review: Environmental and metabolic factors affecting aminoglycoside efficacy. World Journal of Microbiology and Biotechnology, 39,

7. https://doi.org/10.1007/s11274-022-03445-8

43. Shalev-Benami, M., Zhang, Y., Rozenberg, H., Nobe, Y., Taoka, M., Matzov, D., Zimmerman, E., Bashan, A., Isobe, T., Jaffe, C. L., et al. (2017). Atomic resolution snapshot of Leishmania ribosome inhibition by the aminoglycoside paromomycin. Nature Communications, 8, 1589. https://doi.org/10.1038/s41467-017-01664-4

44. Maarouf, M., De Kouchkovsky, Y., Brown, S., Petit, P. X., & Robert-Gero, M. (1997). In vivo interference of paromomycin with mitochondrial activity of Leishmania. Experimental Cell Research, 232, 339–348. https://doi.org/10.1006/excr.1997.3500

45. Kimutai, R., Musa, A. M., Njoroge, S., Omollo, R., Alves, F., Hailu, A., Khalil, E. A. G., Diro, E., Soipei, P., Musa, B., et al. (2017). Safety and effectiveness of sodium stibogluconate and paromomycin combination for the treatment of visceral leishmaniasis in Eastern Africa: Results from a pharmacovigilance programme. Clinical Drug Investigation, 37, 259–272. https://doi.org/10.1007/s40261-016-0481-0

46. Sundar, S., Singh, A., Agrawal, N., & Chakravarty, J. (2019). Effectiveness of single-dose liposomal amphotericin B in visceral leishmaniasis in Bihar. The American Journal of Tropical Medicine and Hygiene, 101, 795. https://doi.org/10.4269/ajtmh.19-0179

47. Heidari-Kharaji, M., Rodrigues, P., & Petersen, C. (2025). Solid lipid nanoparticles encapsulated with paromomycin: An effective oral formulation against Leishmania major in mouse model. Parasitology Immunology, 47, e70002. https://doi.org/10.1111/pim.70002

48. Kamiński, D. M. (2014). Recent progress in the study of the interactions of amphotericin B with cholesterol and ergosterol in lipid environments. European Biophysics Journal, 43, 453–467. https://doi.org/10.1007/s00249-014-0983-8

49. Readio, J. D., & Bittman, R. (1982). Equilibrium binding of amphotericin B and its methyl ester and borate complex to sterols. Biochimica et Biophysica Acta (BBA)—Biomembranes, 685, 219–224. https://doi.org/10.1016/0005-2736(82)90103-1

50. Gruszecki, W. I., Gagos, M., & Kernen, P. (2002). Polyene antibiotic amphotericin B in monomolecular layers: Spectrophotometric and scanning force microscopic analysis. FEBS Letters, 524, 92–96. https://doi.org/10.1016/S0014-5793(02)03009-0

51. Kumari, S., Kumar, V., Tiwari, R. K., Ravidas, V., Pandey, K., & Kumar, A. (2022). Amphotericin B: A drug of choice for visceral leishmaniasis. Acta Tropica, 235, 106661. https://doi.org/10.1016/j.actatropica.2022.106661

52. Mondal, D., Alvar, J., Hasnain, M. G., Hossain, M. S., Ghosh, D., Huda, M. M., Nabi, S. G., Sundar, S., Matlashewski, G., & Arana, B. (2014). Efficacy and safety of single-dose liposomal amphotericin B for visceral leishmaniasis in a rural public hospital in Bangladesh: A feasibility study. The Lancet Global Health, 2, e51–e57. https://doi.org/10.1016/S2214-109X(13)70118-9

53. Wijnant, G. J., Dumetz, F., Dirkx, L.,

Bulté, D., Cuypers, B., Van Bocxlaer, K., & Hendrickx, S. (2022). Tackling drug resistance and other causes of treatment failure in leishmaniasis. Frontiers in Tropical Diseases, 3, 837460. https://doi.org/10.3389/fitd.2022.837460

54. Frézard, F., Aguiar, M. M. G., Ferreira, L. A. M., Ramos, G. S., Santos, T. T., Borges, G. S. M., Vallejos, V. M. R., & De Morais, H. L. O. (2023). Liposomal amphotericin B for treatment of leishmaniasis: From the identification of critical physicochemical attributes to the design of effective topical and oral formulations. Pharmaceutics, 15, 99. https://doi.org/10.3390/pharmaceutics15010099

55. Cirri, D., Chiaverini, L., Pratesi, A., & Marzo, T. (2022). Is the next cisplatin already in our laboratory? Comments on Inorganic Chemistry, 43, 465–478. https://doi.org/10.1080/02603594.2022.2152016

56. Bhatt, P., Singh, S., Garg, S., Ashoka, P., Mishra, S. K., Kaushik, S., … Kumar, V. (2025). Impact of cross-linking on the physicochemical and physiological characteristics of barnyard millet (Echinochloa frumentacea) grains starch. Die Starke, 77(1). doi:10.1002/star.202300285

57. Chugh, B., Dwivedi, K., Garg, P., Bhatt, P., & Gupta, S. (2025, August 14). IoT integration in health sciences. Blockchain in Health Sciences, pp. 29–48. doi:10.1002/9781394336043.ch2

58. Fatima, Z., Noor, A., Bhatt, P., Sethi, V. A., & Gupta, C. (2026). Formulation and evaluation of a quercetin-loaded nanoemulgel for targeted topical treatment of rheumatoid arthritis. BioNanoScience, 16(2). doi:10.1007/s12668-025-02344-0

59. Sadhu, P. S., Bandyopadhyay, S. N., Toro, P. D., Raj, R., Maurya, A. K., Shrivastava, A., … Bhatt, P. (2026). IN VIVO PHARMACOLOGICAL PROFILING, BIOAVAILABILITY AND ACUTE TOXICITY ASSESSMENT OF MELOXICAM IN SITU HYDROGELS UTILIZING LEPIDIUM SATIVUM BIOPOLYMER IN WISTAR RATS. Journal of Experimental Zoology India, 29(2), 1529–1537. doi:10.51470/jez.2026.29.2.1529

60. Singh, P. K., Kumar, V., Parihar, A., Goyal, G., Singh, S., & Bhatt, P. (2026). Advancing formulation development with AI: ANN-driven modeling and optimization of etodolac extended-release tablets. Journal of Pharmaceutical Innovation, 21(4). doi:10.1007/s12247-026-10539-5

61. Tomar, S., Bhatt, P., Kumar, V., Tyagi, L. K., Sethi, V. A., Sharma, K. K., … Kumar, M. (2026). Modification of pearl millet (Pennisetum glaucum) starch: Cross-linking, physicochemical and toxicity studies. Die Starke, 78(5). doi:10.1002/star.70207

62. Chiaverini, L., Di Leo, R., Famlonga, L., Pacini, M., Baglini, E., Barresi, E., Peana, M. F., Tolbatov, I., Marrone, A., La Mendola, D., et al. (2025). The metal(loid)s' dilemma: What's the next step for a new era of inorganic molecules in medicine? Metallomics, 17, 13. https://doi.org/10.1093/mtomcs/mfaf013

63. Cirri, D., Bartoli, F., Pratesi, A., Baglini, E., Barresi, E., & Marzo, T. (2021). Strategies for the improvement of metal-based

chemotherapeutic treatments. Biomedicines, 9, 504. https://doi.org/10.3390/biomedicines9050504

64. Roder, C., & Thomson, M. J. (2015). Auranofin: Repurposing an old drug for a golden new age. Drugs R&D, 15, 13–20. https://doi.org/10.1007/s40268-015-0083-y

65. Ma, J., van de Sande, W., & Biersack, B. (2025). Exploring a therapeutic gold mine: The antifungal potential of the gold-based antirheumatic drug auranofin. International Journal of Molecular Sciences, 26, 7909. https://doi.org/10.3390/ijms26167909

66. Smith, D. A., Beaumont, K., Maurer, T. S., & Di, L. (2018). Relevance of half-life in drug design. Journal of Medicinal Chemistry, 61, 4273–4282. https://doi.org/10.1021/acs.jmedchem.7b00969

67. Li, H., Hu, J., Wu, S., Wang, L., Cao, X., Zhang, X., Dai, B., Cao, M., Shao, R., Zhang, R., et al. (2016). Auranofin-mediated inhibition of PI3K/AKT/MTOR axis and anticancer activity in non-small cell lung cancer cells. Oncotarget, 7, 3548–3558. https://doi.org/10.18632/oncotarget.6516

68. Kupersmith, M. J., & Jette, N. (2023). Specific recommendations to improve the design and conduct of clinical trials. Trials, 24, 263. https://doi.org/10.1186/s13063-023-07276-2

69. Wang, J., Yu, B., Dou, Y. N., & Mascaro, J. (2024). Biomarker-driven oncology trial design and subgroup characterization: Challenges and potential solutions. JCO Precision Oncology, 8, e2400116. https://doi.org/10.1200/PO.24.00116

70. Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., Doig, A., Guilliams, T., Latimer, J., McNamee, C., et al. (2018). Drug repurposing: Progress, challenges and recommendations. Nature Reviews Drug Discovery, 18, 41–58. https://doi.org/10.1038/nrd.2018.168

71. Okuyama, R. (2023). Advancements in drug repurposing: Examples in psychiatric medications. International Journal of Molecular Sciences, 24, 11000. https://doi.org/10.3390/ijms241311000

72. Bhati, N., Bhatt, P., Kumar, V., Tomar, S., Sethi, V. A., Mittal, A., … Tyagi, L. K. (2025). Eco-friendly enzymatic starch modification: Precision strategies for tailored industrial and biomedical functionalities. Die Starke, 77(9). doi:10.1002/star.70087

73. Bhatt, P., Kumar, V., Kumar, M., Singh, S., Garg, S., & Ali, S. S. (2025). Development and characterization of sodium tripolyphosphate-crosslinked Echinochloa esculenta (Ghingora) starch microspheres as potential drug carrier. International Journal of Biological Macromolecules, 323(Pt 1), 146807. doi:10.1016/j.ijbiomac.2025.146807

74. Bhatt, P., Kumar, V., Singh, S., Garg, S., Kumar, M., Wong, L. S., … Subramaniyan, V. (2025). Enzymatic debranching of starch: Techniques for improving drug delivery and industrial applications. Die Starke, 77(4). doi:10.1002/star.202400224

75. Bhatt, P., Patil, A., Ranjana, Soni, S., & Bagal, Y. S. (2025). Cyclodextrin nanoparticles: A new frontier in molecular detection. In Cyclodextrins for Chemosensing (pp. 249–274).

Cham: Springer Nature Switzerland.

76. Deben, C., Boullosa, L. F., Fortes, F. R., De La Hoz, E. C., Le Compte, M., Seghers, S., Peeters, M., Vanlanduit, S., Lin, A., Dijkstra, K. K., et al. (2024). Auranofin repurposing for lung and pancreatic cancer: Low CA12 expression as a marker of sensitivity in patient-derived organoids, with potentiated efficacy by AKT inhibition. Journal of Experimental & Clinical Cancer Research, 43, 88. https://doi.org/10.1186/s13046-024-03012-z