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REVIEW ARTICLE

SCAFFOLD-BASED NANOMEDICINE FOR CANCER, DIABETES, AND MALARIA IN EAST AFRICA: A COMPARATIVE REVIEW OF TRANSLATIONAL BOTTLENECKS AND REGULATORY READINESS

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Abstract

Cancer, type 2 diabetes, and malaria impose a triple pharmacological burden on East Africa. In 2022, sub-Saharan Africa recorded an estimated 118,000 new cervical cancer cases and 76,000 cervical cancer deaths, and Kaposi's sarcoma incidence in Southern and Eastern Africa is far above the global average. Type 2 diabetes is rapidly increasing in the region and carries the world's highest proportion of undiagnosed cases. In 2023, the WHO African Region accounted for approximately 95% of the world's 597,000 malaria deaths. This review compares six such scaffolds platinum-based DNA-crosslinking agents and tubulin-binding stilbenes for cervical cancer and Kaposi's sarcoma, the biguanide core and dietary flavonoids for type 2 diabetes, and the artemisinin endoperoxide and 4-aminoquinoline cores for malaria against the general logic of nanocarrier drug delivery established by landmark work on the enhanced permeability and retention (EPR) effect, ligand-targeted nanocarriers, and the first FDA-approved nanomedicine, liposomal doxorubicin. In preclinical models, nanocarrier reformulation has been shown to improve pharmacokinetic parameters and reduce off-target toxicity for several of the scaffolds discussed, though outcomes vary by platform and disease and clinical confirmation remains limited; median tumour-accumulation efficiency for nanoparticles remains below 1% of the administered dose even for the most clinically advanced platforms, and artemisinin partial resistance driven by *Plasmodium falciparum* kelch13 mutations is now confirmed in Rwanda, Uganda, Eritrea, Tanzania, and beyond. Study conclude by proposing a four-criterion prioritization framework burden fit, bottleneck match, manufacturing feasibility, and regulatory tractability for scaffold–nanocarrier candidates suited to the health-systems realities of Tanzania and the wider East African Community.

Keywords: cancer, diabetes, East Africa, malaria, nanocarriers, scaffold-based drug design, Tanzania.

INTRODUCTION

Cancer, diabetes, and malaria rarely appear together in a single therapeutics review, yet in the East African Community (EAC) they compete for the same constrained pool of regulatory capacity, manufacturing infrastructure, and health financing. Considered separately, each disease has produced a mature body of medicinal chemistry built around a handful of privileged scaffolds[1]. Considered together, a pattern emerges, though not an identical one: each scaffold has demonstrated pharmacological activity in preclinical or clinical studies, but its clinical utility is constrained by one or more of three distinct problem types poor aqueous solubility and bioavailability, dose-limiting systemic toxicity, or the gradual erosion of efficacy through resistance and these problem types differ mechanistically across the three diseases (systemic chemotherapy toxicity, oral antidiabetic pharmaco-kinetics, and transporter- or target-mediated anti-malarial resistance are not interchangeable phenomena)[2]. Nanotechnology has been proposed as a broadly applicable formulation strategy for problems of this kind: encapsulating a scaffold in a liposome, polymeric nanoparticle, or related carrier can prolong circulation, concentrate drug at the diseased tissue via the enhanced permeability and retention (EPR) effect first described in tumour models, and, for several of the scaffolds discussed here, alter the toxicity profile in ways that are often, but not always, favourable

PEGylated liposomal doxorubicin, for instance, reduces cardiotoxicity relative to free doxorubicin but introduces a distinct dose-limiting toxicity of its own (palmar-plantar erythrodysesthesia)[3], illustrating that nanocarriers typically reshape rather than eliminate toxicity. This review asks whether that broader promise holds up, in comparable terms, across cancer, diabetes, and malaria, and what the comparison implies for translational priorities in Tanzania and the wider EAC.

Literature search strategy and selection criteria

This narrative review was conducted through a structured literature search of PubMed, Scopus, and Google Scholar for records published between January 2000 and June 2026, with search emphasis on the period 2018–2026 to prioritise current formulation and resistance data. Search terms combined disease-specific keywords ("cervical cancer", "Kaposi's sarcoma", "type 2 diabetes", "malaria") with scaffold names ("cisplatin", "combretastatin", "metformin", "flavonoid" OR "quercetin", "artemisinin", "chloroquine" OR "piperaquine") and nanocarrier-related terms ("liposome", "PLGA nanoparticle", "chitosan nanoparticle", "metal–organic framework"), combined with Boolean AND/OR operators (e.g., "cisplatin" AND "nanoparticle" AND "cervical cancer"). Reference lists of retrieved articles were hand-searched for additional relevant studies, and regulatory and health-burden statistics were supplemented with reports from the World Health Organization, the International Diabetes Federation, and the African Medicines Agency. Only English-language, peer-reviewed articles were included; preprints were included only where no peer-reviewed equivalent existed. Preclinical (*in vitro* and *in vivo*) and clinical studies were eligible if they reported original data on a nanocarrier formulation of one of the six target scaffolds, or original epidemiological or regulatory data relevant to the three disease areas in East Africa. Studies were screened by title and abstract, and relevant full texts were reviewed for data extraction. As this is a narrative rather than a systematic review, no formal quality-assessment instrument or meta-analysis was applied, no PRISMA flow diagram was generated, and the selection is therefore not exhaustive; the differing depth of evidence available for each scaffold (for example, five formulation studies for cisplatin versus one each for combretastatin and metformin) is itself reported. Because narrative reviews carry an inherent risk of selective citation, conclusions in this review are deliberately framed at the level of mechanistic plausibility and preclinical evidence rather than as claims of established clinical benefit unless a cited study was itself clinical.

Disease burden in East Africa: Why these three diseases, together

The case for treating these three diseases as a single translational problem rests on their overlapping and disproportionate burden in the region. GLOBOCAN 2022 data place cervical cancer as the leading cancer by incidence in Eastern Africa and identify Southern Africa as having the highest cervical cancer incidence of any world subregion, while Kaposi's sarcoma incidence in Southern Africa is dramatically elevated relative to the rest of the continent[4], a pattern confirmed by long-running East African cohort data showing Kaposi's sarcoma incidence rates around 334 per 100,000 person-years among HIV-infected adults in Kenya and Uganda[5], and by sub-Saharan-Africa-wide trend analyses documenting rising cervical cancer incidence in several Eastern and Southern African countries even as it declines elsewhere[6]. Type 2 diabetes, once considered rare in the region, is now well established, with the International Diabetes Federation's Africa region carrying the lowest per-country diagnostic capacity and the highest proportion of undiagnosed cases of any IDF region[7-9], a transition driven by rapid urbanisation and shifting body composition rather than the genetic risk factors more studied in higher-income settings[10], and complicated by pooled continental data showing that most people with diabetes in sub-Saharan Africa remain undiagnosed or inadequately treated[11]. Malaria remains the most severe of the three in absolute terms: the WHO African Region accounted for approximately 95% of the world's 597,000 malaria deaths in 2023[12], a burden that two decades of vector control and case management had substantially reduced from its early-2000s peak[13] before the emergence of partial artemisinin resistance began to erode those gains in parts of East Africa specifically, including confirmed resistance markers in Rwanda, Uganda, Eritrea, and Tanzania[14-16]. Taken together, these three disease burdens do not merely coexist in the same health systems; they share the same underlying translational bottleneck, which is the subject of the remainder of this review.

Scaffold-Level Medicinal Chemistry: Cancer

Platinum-based DNA-crosslinking cores (cisplatin analogs)

Cisplatin and its analogues are the backbone of chemotherapy for cervical cancer. The scaffold is a platinum(II) coordination complex whose activity depends on aquation of its chloride ligands, enabling covalent crosslinking of purine bases in DNA and triggering apoptosis in rapidly dividing cells (mitochondrial damage and oxidative stress contribute additional, less-characterized mechanisms).

Specifically, sequential aquation of the square-planar cis-diamminedichloroplatinum (II) complex in the low-chloride intracellular environment generates a reactive electrophile that forms a 1,2-intrastrand Pt–GpG cross-link, distorting the DNA double helix and blocking replication and transcription; this same reactivity underlies both the drug's efficacy and its dose-limiting toxicity. However, this reactivity is unselective: nephrotoxicity, neurotoxicity, and myelosuppression are the principal factors limiting the dose that can be delivered. A growing body of nanocarrier work, still confined to preclinical (cell-culture and rodent) models for this indication, has targeted this pharmacokinetic and toxicological limitation directly, aiming to confine that reactivity to tumour tissue. Chitosan-coated solid lipid nanoparticles loaded with cisplatin achieve controlled release and lower half-maximal inhibitory concentration (IC50) values in cervical carcinoma (HeLa) cells than the free drug[17], PEGylated liposomal

cisplatin improves both efficacy and safety margins *in vitro* and *in vivo* relative to the free drug[18], and ligand-directed variants for example estrone-conjugated PEGylated liposomal cisplatin, which exploits oestrogen receptors over-expressed on cervical tumour cells achieve stronger tumour-specific cellular uptake via caveolin-mediated endocytosis and improved *in vivo* tumour targeting relative to untargeted formulations[19]. The same estrone-targeting logic extends to co-delivery platforms for related gynaecological cancers, where PEGylated liposomes co-loaded with paclitaxel and carboplatin reduce the acute toxicity associated with the free drug combination[20], and to injectable PEGylated chitosan nano/sub-micron crystal formulations of cisplatin designed for improved physicochemical stability and reduced cytotoxic burden on healthy tissue[21]. None of these five formulations has yet been evaluated in a registered clinical trial for cervical cancer, so the efficacy and safety gains described here should be read as preclinical evidence of concept rather than demonstrated clinical benefit.

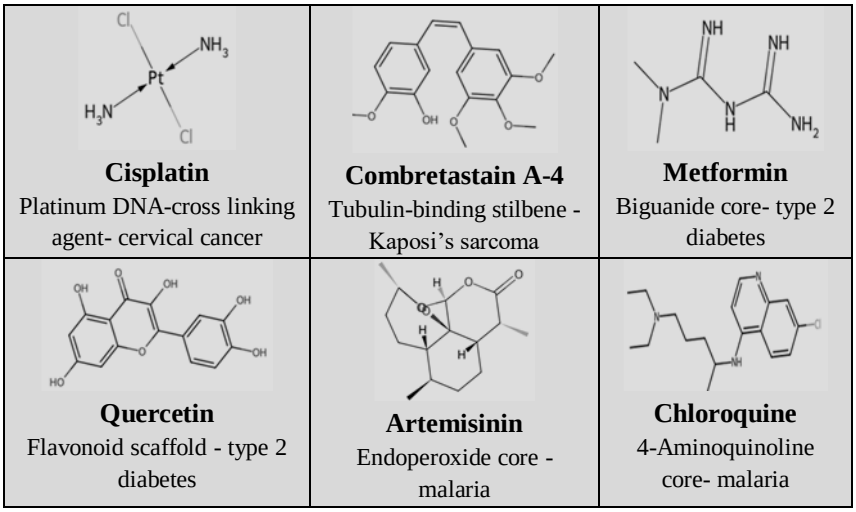

Figure 1: Chemical structures of the lead scaffolds.

Tubulin-binding stilbenes (combretastatin-type scaffolds)

Kaposi's sarcoma (KS), an angiogenesis-driven malignancy with disproportionately high incidence in East and Southern Africa[4,5], is mechanistically distinct from cervical cancer and calls for a different scaffold. Combretastatin A-4 and its water-soluble phosphate prodrug, both derived from the stilbene skeleton of the African tree *Combretum caffrum*, bind tubulin at the colchicine site and selectively destabilize the immature microtubule networks of proliferating tumour endothelium; the (Z)-configured (cis) stilbene skeleton is essential for this activity, since the corresponding (E)-isomer is markedly less active. In endothelial cells this produces mitotic arrest at metaphase followed by caspase-independent mitotic cell death, giving the scaffold a vascular-disrupting mechanism that is complementary to, rather than overlapping with, the DNA-damage mechanism of platinum agents[22]. Because the parent compound is rapidly cleared and has a narrow therapeutic window, it is a natural candidate for nanocarrier-based half-life extension and tumour-vasculature targeting, an area that remains comparatively under-explored relative to cisplatin nanoformulations and represents a clear regional research gap given the concentration of KS burden in Southern and Eastern Africa.

General nanocarrier principles underlying both cancer scaffolds

Both cancer scaffolds sit within a broader nanocarrier logic first articulated for macromolecular anticancer agents almost four decades ago, when tumoritropic accumulation of proteins and polymer–drug conjugates via leaky tumour vasculature was first described as the enhanced permeability and retention effect[1]. This effect arises because discontinuous, fenestrated tumour endothelium and impaired lymphatic drainage allow nanocarriers whether liposomes encapsulating hydrophilic drug within an aqueous core bounded by a phospholipid bilayer, polymeric (PLGA±chitosan) nanoparticles dispersing drug through a biodegradable polymer matrix, or metal organic frameworks (MOFs) loading drug within a porous crystalline lattice of metal nodes and organic linkers to accumulate passively in tumour tissue, in contrast to free drug, which diffuses uniformly into healthy tissue and drives systemic toxicity. That principle underwrote the clinical translation of PEGylated liposomal doxorubicin (Doxil), the first FDA-approved nanomedicine, whose reduced cardiotoxicity relative to free doxorubicin established the template that later cisplatin and combretastatin nanoformulations have followed[2,3], and it was subsequently generalised into a broader framework for ligand-targeted nanocarrier design across tumour types[23]. Polymeric platforms particularly poly(lactic-co-glycolic acid) (PLGA), whose biodegradability and FDA-approved status have made it one of the most widely used nanocarrier materials in oncology[24-26], often modified with chitosan to improve encapsulation efficiency and moderate initial burst release[27] provide an alternative to lipid-based carriers that is generally reported as lower-cost in the manufacturing literature, although region-specific costing data for East African production have not been

published and this potential advantage should be treated as plausible rather than established for the region. However, a landmark meta-analysis of nanoparticle biodistribution across a decade of published studies found that only a median of 0.7% of the administered nanoparticle dose accumulates in a solid tumour, regardless of platform[28] a tumour-accumulation efficiency, not a measure of therapeutic effect a finding that tempers expectations for any new scaffold–nanocarrier pairing discussed in this review. The EPR effect itself is also increasingly recognized as inconsistent: it is more pronounced and more reproducible in the rodent xenograft models from which it was originally characterized than in human tumours, which are more heterogeneous, less leaky, and subject to elevated interstitial pressure that can oppose nanoparticle penetration.

Mechanistic basis of carrier selection: Passive targeting, active targeting, and controlled release

The six scaffolds in this review are matched to three carrier chemistries liposomes, PLGA/chitosan polymeric nanoparticles, and metal–organic frame-works (MOFs) and each chemistry operatio-nalises a distinct combination of targeting and release principles that determines whether it can plausibly improve a given scaffold's efficacy. Passive targeting relies on nanocarrier size (typically 10–200 nm) to exploit pathophysiological differences between diseased and healthy tissue: in tumours this is the EPR effect described above; systemic circulation time is itself a carrier property, since uncoated nanoparticles are rapidly opsonised by serum proteins and cleared by the mononuclear phagocyte system, which is why PEGylation grafting polyethylene glycol chains onto the carrier surface is used across all three cancer- and malaria-relevant liposomal formulations to create a hydrophilic "stealth" layer that delays protein adsorption and extends half-life from minutes to hours[2,3]. Active targeting adds a ligand (an antibody fragment, peptide, or small molecule such as the estrone used in the cisplatin formulations) to the carrier surface so that receptor-mediated endocytosis, rather than passive accumulation alone, concentrates the carrier in cells that over-express the cognate receptor [19,23]; this is a meaningfully different mechanism from passive EPR-based accumulation and is the reason ligand-targeted formulations can outperform untargeted ones even when both rely on the same underlying nanoparticle chemistry.

Controlled release is the second axis along which these carriers differ, and it is this axis, rather than targeting, that is most relevant to the largely oral, chronic-disease scaffolds. Liposomes release their aqueous-core cargo as the phospholipid bilayer is remodelled or destabilised *in vivo* (by serum lipoproteins, local pH, or, in triggered designs, temperature or enzymatic cleavage), giving release kinetics that are relatively fast and difficult to sustain beyond hours to a few days. PLGA nanoparticles release drug more slowly and more tunably, through a combination of diffusion through the polymer matrix and hydrolytic erosion of the lactide:glycolide backbone into lactic and glycolic acid; the lactide:glycolide ratio and particle size can be varied to shift release from days to weeks[24-26], and surface modification with chitosan a cationic, muco-adhesive polysaccharide improves encapsulation efficiency, moderates the initial burst release common to PLGA systems, and confers mucoadhesive and permeation-enhancing properties that are particularly relevant to oral and mucosal delivery of peptides and small molecules alike[27-29]. Metal–organic frameworks depart from both polymeric mechanisms: drug is loaded within a porous crystalline lattice of metal ions or clusters connected by organic linkers, and release is governed by framework degradation (hydrolysis or ligand exchange at the metal node) rather than polymer erosion, which can yield very high drug-loading capacity and multi-day sustained release metformin-loaded MOFs achieve release over roughly 96 hours *in vitro*[30] but, introduces a materials-safety question that biodegradable organic carriers do not share, namely the fate of the metal nodes themselves after the framework degrades.

Matching mechanism to bottleneck therefore means asking, for each scaffold, whether its dominant limitation is one that a carrier's size and surface chemistry alone can fix (a passive-targeting or controlled-release problem) or one that requires an added ligand or co-delivered second agent (an active-targeting or combination-delivery problem) a distin-ction developed scaffold-by-scaffold and drawn together, disease by disease.

Scaffold-level medicinal chemistry: Type 2 diabetes biguanide core (metformin)

Metformin a small, highly polar, renally cleared dimethylbiguanide remains first-line therapy for type 2 diabetes, the dominant form of diabetes in the EAC[7,8], acting mainly through inhibition of hepatic gluconeo-genesis and improved peripheral insulin sensitivity. Its small, polar structure underlies both its short plasma half-life and its favourable safety margin: oral bioavailability is only 40–60%, plasma half-life is short, and gastrointestinal intolerance is common, all of which push patients toward high, frequent dosing in a region where the majority of people with diabetes are already undiagnosed or under-treated[9,11]. Nanocarrier reformulation directly targets this pharmacokinetic weakness rather than the pharmacodynamic mechanism: in a single *in vitro* study, metformin loaded into a metal–organic framework (MOF) nanocarrier achieved sustained release over roughly 96 hours and, in parallel, reduced hyperglycaemia-associated inflammatory signalling and restored endothelial nitric oxide synthase activity in cultured vascular endothelial cells, pointing to a possible nanocarrier benefit that extends beyond bioavailability to the vascular complications of diabetes[30]; this remains a single preclinical report and has not been replicated or tested *in vivo* for chronic dosing. This dual effect pharmacokinetic correction plus a vasculo-protective bystander effect is a pattern worth testing for the other scaffolds discussed here, and echoes the oral-delivery logic developed for insulin itself, where chitosan-based nanoparticles and microparticles have been the most extensively studied carrier class for overcoming gastric degradation and improving

intestinal absorption of peptide thera-peutics[29], a technology base that could plausibly be redirected toward small-molecule antidiabetics such as metformin. Metal-organic-framework and chitosan nanocarriers are, correspondingly, the platforms best positioned to target metformin's dosing-frequency and bioavailability limitations.

A critical note on metal–Organic framework safety for chronic oral use

The MOF result above is encouraging but should not be read as evidence that MOFs are a safe platform for the daily, decades-long dosing that type 2 diabetes management requires. Most reported MOFs are built from transition-metal nodes (commonly zirconium, zinc, iron, or copper) connected by organic linkers, and while the intact framework can be biocompatible, the framework is not inert over a chronic dosing horizon: gradual hydrolytic degradation is precisely the mechanism that releases the encapsulated drug, and the same degradation releases the metal node and organic linker into systemic circulation. Long-term data on the fate, tissue accumulation, and clearance of these degradation products under repeated daily oral dosing are not yet available for the metformin-MOF system cited above, and nanotoxicological guidance for inorganic carriers more broadly remains an active area of concern rather than a resolved question[31]. This stands in contrast to PLGA and chitosan, whose degradation products (lactic acid, glycolic acid, and glucosamine-derived sugars) are endogenous or readily metabolised, giving biodegradable polymeric carriers a materially better-characterised chronic safety margin at present. Before a MOF-based antidiabetic candidate could be prioritised under the framework, it would need chronic (multi-month) toxicology data ideally including metal-node biodistribution and renal/hepatic clearance studies a requirement this review flags explicitly rather than assumes will be satisfied.

Flavonoid/polyphenol scaffolds

A complementary, and regionally distinctive, scaffold class comes from dietary and medicinal-plant flavo-noids such as quercetin and its glycosides. The quercetin flavonol backbone a chromen-4-one fused to a catechol-substituted phenyl ring confers dual alpha-glucosidase/alpha-amylase inhibitory activity but suffers from poor aqueous solubility and rapid first-pass metabolism. Rather than targeting hepatic glucose output, these compounds inhibit the intestinal enzymes α-glucosidase and α-amylase, slowing carbohydrate digestion and blunting postprandial glucose spikes. A recent systematic review of 974 curated flavonoid structures identified 177 compounds with dual inhibitory activity against both enzymes, several of which outperform the reference inhibitor acarbose *in vitro*[32]. Because flavonoids are typically poorly absorbed and rapidly metabolized, they are strong candidates for oral nanocarrier delivery using the same chitosan and PLGA platforms already validated for insulin and cisplatin[27,29], and the presence of flavonoid-rich plant species in East African flora suggests a plausible, though as yet unproven, regional sourcing opportunity phytochemical extraction and local formulation that platinum, stilbene, and biguanide scaffolds do not share; realising this opportunity would require region-specific evidence on which plant sources, compound abundance, extraction standar-disation, and supply-chain sustainability are actually viable, none of which is yet established in the cited literature. This matters given that the epidemiological transition driving type 2 diabetes in sub-Saharan Africa is now well documented across pooled multi-country data[11] and is expected to intensify as urbanization continues[7,10].

Scaffold-Level Medicinal Chemistry: Malaria

Artemisinin endoperoxide core

Artemisinin and its semisynthetic derivatives remain the anchor of first-line malaria treatment through artemisinin-based combination therapy (ACT). The scaffold's tetracyclic 1,2,4-trioxane skeleton carries a labile endoperoxide (O–O) bridge whose activity depends on cleavage by parasite haem iron: parasite Fe(II)-haem cleaves the O–O bond to generate a carbon-centred radical that alkylates parasite proteins, producing rapid killing but leaving the short pharmacokinetic half-life that is implicated below in resistance selection. Poor aqueous solubility, a short elimination half-life, and the molecular marker for artemisinin resistance identified in Southeast Asian *P. falciparum* kelch13 mutants[33] subsequently confirmed to have emerged independently in Rwanda[14] and now documented across Uganda, Eritrea, and Tanzania[15,16], with continued spread reported as recently as 2025 in western Uganda[34] have all motivated nanocarrier reformulation; ACT (artemisinin-based combination therapy) pairs a fast-acting artemisinin derivative with a longer-acting partner drug such as piperaquine,. Polymeric and lipid nanoparticle encapsulation of artemisinin derivatives has been shown to improve oral bioavailability and antiplasmodial efficacy relative to the free drug across multiple *in vitro* and *in vivo* models[35].

By smoothing out the pharmacokinetic troughs associated with the drug's short half-life, sustained-release nano formulations are proposed here as one plausible route to reducing sub-therapeutic parasite exposure. This should be read as an untested mechanistic hypothesis rather than a demonstrated benefit: no cited study has shown that a sustained-release artemisinin nanoformulation actually slows or prevents the *in vivo* selection of kelch13 mutants, and confirming or refuting this hypothesis would require dedicated resistance-selection studies. The stakes of resolving it are nonetheless high, given how much of the malaria mortality reduction achieved between 2000 and 2015[13] is now at risk from the spread of these mutations within East Africa specifically.

4-Aminoquinoline core (chloroquine/piperaquine)

The 4-aminoquinoline scaffold, used historically as chloroquine and today mainly as the ACT partner drug piperaquine, acts by inhibiting haem detoxification inside the parasite digestive vacuole. This scaffold provides the clearest resistance-comparison case in the review: point mutations in the *P. falciparum* chloro-quine resistance transporter (PfCRT) confer resistance to piperaquine through an altered drug-binding and efflux mechanism that is mechanistically distinct from

the radical-mediated resistance seen with artemisinin[36], and specific PfCRT haplotypes that emerged in Southeast Asia and raise piperaquine resistance can simultaneously restore chloroquine susceptibility, illustrating a genuine evolutionary trade-off within the same transporter[37]. Because 4-aminoquinoline resistance is transporter-mediated rather than a metabolism or solubility problem, nano-carrier strategies built around bioavailability enhancement alone are unlikely to address it. Combination-delivery vehicles that co-encapsulate an efflux-pump modulator with the drug are conceptually attractive, but this review is not aware of a specific, chemically defined PfCRT efflux modulator with validated proof-of-concept co-encapsulation data; the proposal should therefore be read as identifying an unresolved preclinical research need for combination nanocarrier design against transporter-mediated resistance rather than as an existing or imminent solution, an important distinction for the comparative framework below. The World Health Organization's most recent malaria reporting explicitly flags this resistance dynamic as a first-order threat to the continued efficacy of artemisinin-based combination therapy across the region[12].

Comparative analysis: Nanocarriers and shared translational challenges

Laid side by side, the six scaffolds fall into two functional categories with respect to what a nanocarrier is actually being asked to fix. For cisplatin, metformin, and artemisinin, the dominant problem is pharmacokinetic poor solubility, rapid clearance, or a narrow therapeutic index and nanocarrier encapsulation directly targets that problem with a consistent playbook of liposomes, polymeric nanoparticles, or metal–organic frameworks[17-19,30,35]. For combretastatin and 4-aminoquinolines, the limitation is mechanistic a narrow window between vascular-disrupting and normal-tissue effects, or transporter-mediated resistance and here nanocarrier design needs to add targeting or combination delivery logic rather than solubility enhancement alone[22,36,37]. Flavonoids sit in between: their poor absorption is a delivery problem, but their mechanism (enzyme inhibition at the gut lumen) also opens the door to non-systemic, gut-targeted nanocarrier designs built on the same chitosan chemistry already validated for oral insulin[29,32], a design space that is, at minimum, a poorer fit for the other five scaffolds gut-targeted, non-systemic delivery is not exclusive to flavonoids (chitosan- and PLGA-based oral platforms have also been explored for artemisinin derivatives, for example[35]), but it is the flavonoid mechanism specifically, rather than the carrier chemistry, that makes purely local gut action pharmacologically sufficient; the other five scaffolds require systemic exposure to reach their target tissue and so cannot rely on gut-local action alone.

Read across the six scaffolds, this comparison also maps onto a single translational-bottleneck spectrum: cisplatin, metformin, and artemisinin sit toward the pharmacokinetic end, where encapsulation alone addresses the main limitation, while combretastatin and the 4-aminoquinolines sit toward the mechanistic end, where nanocarrier design must add targeting or combination-delivery logic; flavonoids occupy an intermediate position, since their gut-local mechanism is amenable to carrier retention rather than either strategy alone. First, the overwhelming majority of the evidence base for every scaffold nanocarrier pairing discussed here is preclinical cell culture and rodent models with very few candidates that have progressed to registered clinical trials for the specific indications relevant to East Africa; where clinical translation is most advanced, only a median of 0.7% of the administered dose reaches the tumour[28].

Table 1: Comparative summary of the six scaffolds discussed in this review.

Scaffold	Key structural feature	Principal limitation	Limitation type	Proposed nanocarrier	Evidence level	East African relevance
Cisplatin	Pt(II) square-planar complex; labile Cl ligands	Nephro-/neuro-/myelotoxicity from unselective DNA crosslinking	Toxicity (systemic)	PEGylated liposome; estrone-targeted liposome; chitosan SLN	Preclinical (*in vitro*/*in vivo*)[10-14]	Cervical cancer burden and treatment access[16]
Combretastatin A-4	(Z)-stilbene; colchicine-site tubulin binder	Narrow window between vascular disruption and normal-tissue toxicity	Mechanistic/PK	Liposomal / nanoparticle vascular-disrupting formulation	Preclinical, single study[15]	Kaposi's sarcoma incidence disproportionately high[16,18]
Metformin	Dimethylbiguanide, small and highly polar	Low oral bioavailability (40–60%), short half-life, GI intolerance	Pharmacokinetic	Metal–organic framework (sustained release)	Preclinical, single study; safety unresolved[19,37]	Rising, largely undiagnosed T2D burden[23,26]
Quercetin (flavonoids)	Flavonol (chromen-4-one + catechol-phenyl)	Poor absorption; rapid first-pass metabolism	Pharmacokinetic (local mechanism)	Chitosan/PLGA gut-targeted nanoparticle	Systematic review of structures; no primary nanocarrier data[22]	Potential local plant sourcing (unproven)
Artemisinin	Sesquiterpene 1,2,4-trioxane (endoperoxide)	Poor solubility; short half-life; kelch13 resistance	Pharmacokinetic + emerging resistance	Polymeric/lipid nanoparticle (sustained release)	Preclinical review-level evidence[28]	ACT backbone; ART-R spreading in region[29-32]
Chloroquine / piperaquine	4-Aminoquinoline	PfCRT transporter-mediated resistance	Mechanistic (resistance)	Combination nanocarrier with efflux modulator (conceptual, unresolved)	Resistance-mechanism studies only; no nanocarrier proof-of-concept[33,34]	ACT partner drug; resistance a first-order regional threat[36]

Second, nanomedicine characterization particle size, zeta potential, encapsulation efficiency, batch-to-batch reproducibility demands analytical infrastructure that is unevenly distributed even within well-resourced settings, and nanomaterials additionally carry size- and surface-dependent toxicological profiles that differ qualitatively from their bulk-material counterparts and require dedicated hazard assessment rather than extrapolation from conventional small-molecule toxicology[31]. Third, and most directly a policy issue, none of the three diseases benefits from a nano-medicine specific regulatory pathway in the region, which means every candidate is currently evaluated case-by-case under conventional medicines legislation that was not designed for nanoscale critical quality attributes[38,39].

From mechanism to efficacy: Applying nanocarrier principles disease by disease

Cancer (cisplatin, combretastatin). Here the efficacy gain nanocarriers can plausibly deliver is principally about therapeutic index rather than raw potency: cisplatin already kills tumour cells effectively, so the translational problem is confining that cytotoxicity to the tumour. PEGylated liposomal encapsulation extends circulation time and exploits passive EPR-based accumulation to raise the tumour-to-healthy-tissue exposure ratio, while estrone-targeted variants add active, receptor-mediated uptake on top of that passive effect[19]; both mechanisms independently reduce the free-drug concentration reaching the kidney, peripheral nerves, and bone marrow that otherwise cap the dose. For combretastatin, whose efficacy problem is a narrow window between vascular-disrupting activity and normal-tissue toxicity rather than poor solubility per se, the efficacy gain from nanocarrier delivery is expected to come mainly from controlled-release pharmacokinetics that avoid the sharp free-drug concentration spikes associated with narrow-window toxicity, an approach that has direct precedent in other vascular-disrupting agent formulations but remains single-study evidence for this scaffold[22] (Table 1).

Diabetes (metformin, quercetin). For metformin the efficacy-limiting problem is pharmacokinetic low bioavailability and a short half-life driving frequent, high-dose regimens with GI side effects so the relevant nanocarrier principle is sustained release rather than targeting: a carrier that maintains therapeutic plasma concentrations between doses can, in principle, achieve the same glycaemic control with lower peak concentrations and fewer doses, directly addressing the adherence problem that undermines efficacy in under-treated regional populations[9,11,30]. For quercetin and other flavonoids, the mechanism of action itself is local (gut-lumen enzyme inhibition), so the relevant nanocarrier principle is not systemic circulation but gut retention and controlled local release: a mucoadhesive chitosan carrier can in principle keep the inhibitor in contact with the intestinal brush border for longer, improving the postprandial-glucose-lowering effect without requiring the compound to survive first-pass metabolism at all an efficacy route unavailable to a scaffold that must act systemically. Malaria (artemisinin, chloroquine/piperaquine). For the artemisinin endoperoxide, efficacy is already high on a per-dose basis, so the nanocarrier principle most relevant to this scaffold is again sustained release: maintaining haem-triggered radical generation above the parasite-killing threshold for longer would, if the resistance hypothesis holds, improve both cure rates in the present and resistance-selection dynamics over time though, as noted there, this remains a hypothesis rather than demonstrated efficacy. Piperaquine's problem is different in kind: because PfCRT-mediated resistance is a transporter mutation rather than a pharmacokinetic failure, no sustained-release or solubility-enhancing carrier can restore efficacy once resistance is established. The only nanocarrier principle that maps onto this bottleneck is combination delivery co-encapsulating an efflux-pump modulator so that both agents reach the parasite digestive vacuole together and, this principle is mechanistically sound but has no validated chemical implementation yet, making it the clearest example in this review of a bottleneck that nanocarrier engineering alone, absent a suitable co-drug, cannot resolve.

Read across the three diseases, only two nanocarrier principles recur with genuine mechanistic force: sustained/controlled release, which plausibly improves efficacy wherever the limiting problem is pharma-cokinetic (cisplatin, metformin, artemisinin), and active or combination targeting, which is necessary wherever the limiting problem is mechanistic or resistance-based (combretastatin, piperaquine) and cannot be substituted for by better pharmacokinetics alone. Flavonoids occupy a third, narrower category local rather than systemic action that benefits from carrier retention rather than either of the other two principles. This mapping, rather than a single carrier chemistry, is what determines whether a given nanocarrier candidate can be expected to translate into a genuine efficacy gain, and it is the logic underlying the bottleneck-match criterion in the prioritization framework.

Regulatory, manufacturing, and implementation considerations for Tanzania and the EAC

A cross-sectional survey of medicines regulatory authorities across the Southern African Development Community including the Tanzania Medicines and Medical Devices Authority found that regulators are generally aware nanomedicines exist but apply conventional medicines legislation to them by default, and identified limited technical capacity and inter-agency collaboration as the main barriers to developing nanomedicine specific guidance[38]. A parallel continental analysis reaches a similar conclusion: African national regulatory authorities are at markedly different levels of maturity, there is no harmonised nanomedicine framework comparable to the European Medicines Agency's nanomedicine guidelines or the US FDA's nanotechnology guidance for industry, and research–industry–university partnerships capable of carrying a nanomedicine candidate from bench to registration remain scarce[39]. The African Medicines Agency (AMA), established by treaty in 2019 and entering into force in November 2021 following its fifteenth ratification, is intended to coordinate exactly this kind of continental harmonization, building on the

East African Community's own medicines regulatory harmonization initiative, whose pilot phase reduced registration timelines from 24 months to 8–12 months among participating EAC authorities. By 2024, 29 African Union member states had ratified the AMA treaty and the agency had begun early technical operations, but major economies (including Nigeria and South Africa) remain outside the treaty, funding and legal-framework gaps persist across member states, and the agency does not yet have nanomedicine-specific technical guidance of its own[40,41]. For Tanzania and the EAC specifically, this implies that scaffold–nanocarrier candidates advancing toward clinical development will need to budget for regulatory engagement as a first-class work stream including early consultation with national authorities, alignment with existing EAC work-sharing mechanisms, and characterization data generated to a standard that would satisfy a stringent regulatory authority even where the local authority's own guidance is still evolving. A further caveat applies to every formulation study: the great majority was conducted outside East Africa, in academic laboratories in Asia, Europe, and North America. Regional relevance in this review is therefore being assessed on the basis of disease burden, resistance patterns, manufacturing feasibility, and regulatory tractability for the East African context not on the basis that these specific formulations have already been tested in East African populations or manufacturing settings, which for all six scaffolds they have not.

Proposed prioritization framework

The comparative analysis developed indicates that the translational potential of a scaffold–nanocarrier candidate cannot be inferred from any single dimension of evidence considered in isolation: a candidate may be pharmacologically well matched to a burden of substantial regional significance yet remain manufacturing infeasible, or may be readily manufacturable yet lack any credible route to regulatory approval. Accordingly, we propose a four-criterion framework, synthesizing the evidence presented above, for prioritising scaffold–nanocarrier candidates for further development in Tanzania and the wider East African Community (EAC). The four criteria are intended to be applied jointly rather than singly, since a candidate that performs favourably on one dimension while performing poorly on another does not constitute a credible near-term priority, as illustrated for several of the candidates discussed in the concluding synthesis. The first criterion, burden fit, assesses whether a candidate addresses a scaffold deployed against a disease subtype, or a resistance pattern, of documented and substantial regional prevalence for example, cervical cancer and Kaposi's sarcoma within oncology, type 2 diabetes within endocrinology.

Table 2: Regulatory, manufacturing, and implementation considerations for nanocarrier translation in Tanzania and the EAC.

Dimension	Current status in Tanzania (TMDA)	Current status in the EAC / continentally	Implication for scaffold–nanocarrier candidates
Regulatory framework	Applies conventional medicines legislation to nanomedicines by default; no nanomedicine-specific guidance[38]	No EAC-wide nanomedicine framework; AMA does not yet issue nanomedicine-specific technical guidance[39-41]	Budget for case-by-case regulatory engagement; generate characterisation data to a stringent-authority standard even where local guidance is silent
Registration pathway & timelines	National registration via TMDA, informed by regional work-sharing initiatives	EAC medicines harmonisation pilot cut registration timelines from ~24 months to 8–12 months for participating authorities[40]	Favour candidates that can enter existing EAC joint-assessment or work-sharing pathways rather than novel nanomedicine-only routes
Analytical / characterisation capacity	Limited access to routine particle-size, zeta-potential, and encapsulation-efficiency testing at regulatory-grade standard	Unevenly distributed across the region; few laboratories meet stringent-authority nanomaterial characterisation standards[38,39]	Prioritise carrier chemistries (e.g., PLGA/chitosan) with simpler, more transferable characterisation methods over complex inorganic platforms
Manufacturing infrastructure	Limited local sterile/aseptic nanoparticle manufacturing capacity	Regional GMP manufacturing capacity concentrated in a small number of hubs; nanomedicine-specific lines are rare[39]	Weight manufacturing feasibility (Section 8) toward simpler, more scalable platforms (polymeric nanoparticles)
Workforce & technical capacity	Inter-agency collaboration and specialist nanomedicine assessors identified as a specific gap [38]	AMA capacity-building is in early stages; research–industry–university partnerships for bench-to-registration translation remain scarce[39,41]	Early investment in assessor training and academic-industry partnerships is a prerequisite for any candidate, independent of scaffold choice
Health-system implementation	Cold-chain and distribution infrastructure varies markedly between urban and rural facilities	Shared challenge across EAC partner states; affects liposomal (cold-chain-sensitive) candidates more than room-temperature-stable polymeric ones	Favourthermostable formulations (e.g., PLGA/chitosan) for rural deployment; reserve liposomal candidates for facilities with reliable cold chain
Continental harmonisation (AMA)	Tanzania participates in EAC and continental harmonisation initiatives	29 AU member states had ratified the AMA treaty by 2024; major economies remain outside; funding and legal-framework gaps persist[40,41]	Treat AMA as an emerging but not yet operational pathway; near-term registration will still run mainly through national and EAC-level mechanisms

The second criterion, bottleneck match, evaluates whether the nanocarrier design under consideration is mechanistically appropriate to the scaffold's actual translational limitation, rather than representing an encapsulation strategy applied without reference to mechanism. Pharmacokinetic limitations as observed for cisplatin, metformin, and artemisinin are amenable to controlled- or sustained-release carrier chemistries. A candidate that applies a pharmacokinetic solution to a mechanistic problem, or the converse, is judged to fail this criterion regardless of the technical merit of the underlying carrier chemistry. The third criterion, manufacturing feasibility, considers whether the nanocarrier can be produced and characterized using equipment, reagents, and technical expertise realistically available to regional manufacturing partners, as distinct from requiring infrastructure that would need to be imported in its entirety (Table 2).

The fourth criterion, regulatory tractability, asks whether a plausible registration pathway exists under current Tanzania Medicines and Medical Devices Authority (TMDA), EAC, and emerging African Medicines Agency (AMA) capacity, or whether a candidate's advancement is instead contingent on nanomedicine specific technical guidance that has not yet been developed. Candidates capable of entering existing EAC joint-assessment or work-sharing arrangements are, at present, more tractable than those that would require the establishment of novel, nanomedicine specific regulatory routes. These four criteria are not proposed as a quantitative scoring instrument no formal weighting scheme is offered, and the relative importance of each criterion may reasonably differ by disease area or funding context.

Limitations of the study

As a narrative rather than a systematic review, no PRISMA flow diagram, formal risk-of-bias instrument, or meta-analysis was applied to the included studies; study selection and synthesis were performed without independent dual screening or extraction, which is a recognized source of interpretive bias in narrative reviews relative to systematic methodologies.

CONCLUSIONS AND RECOMMENDATION

Across cancer, diabetes, and malaria, a consistent translational pattern emerges: these scaffolds are held back less by a lack of pharmacological validity than by pharmacokinetic weaknesses, toxicity profiles, or susceptibility to resistance. Nanocarrier reformulation can address the pharmacokinetic and toxicity-profile problems in preclinical models, but it is not a universal solution: for resistance driven by transporter mutations (piperaquine/PfCRT) or target-site alteration, nanocarrier engineering alone cannot substitute for a chemically distinct co-agent or a modified scaffold. We recommend that East African stakeholders prioritise scaffold–nanocarrier candidates using the four criteria burden fit, bottleneck match, manufacturing feasibility, and regulatory tractability applied jointly rather than singly, since a candidate that scores well on burden fit alone (as all six do) but poorly on manufacturing feasibility or regulatory tractability (as the MOF and combination-delivery candidates currently do) is not yet a credible near-term priority.

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AUTHOR'S CONTRIBUTIONS

Barugahale L: formal analysis, conceptualisation, data organisation, clinical exams, writing original draft. **Mwalongo FO:** data analysis, manuscript writing. **Ndetico KJ:** data analysis, manuscript writing. **Ngalowoka DC:** literature survey. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The related author can provide the empirical data supporting the study's conclusions upon request.

CONFLICT OF INTEREST

There are no conflicts of interest in regard to this project.

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