Repurposing the Antiparasitic Agent Praziquantel for Breast Neoplasm Therapy: A Narrative Review of the Mechanistic Rationale, Current Evidence and Translational Barriers

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Abstract: *Background*: Drug repurposing has become an established route into oncology because agents with a mature safety, pharmacokinetic and manufacturing record can be advanced faster and at lower cost than new chemical entities. Praziquantel, the mainstay of antischistosomal therapy for more than four decades, has been proposed as one such candidate.

Aim: This narrative review examines the case for repurposing praziquantel in breast neoplasia and does so critically rather than promotionally.

Results: Three strands of mechanistic rationale are identified: Praziquantel's target in the parasite is a TRPM channel, raising the untested hypothesis that it might also target the related human TRPM channels linked to breast tumour proliferation, migration and chemoresistance; the R-enantiomer is a partial agonist at the human 5-HT2B receptor, a node in a serotonergic pathway with documented roles in mammary tumour biology; and praziquantel has been proposed to lower the apoptotic threshold of carcinoma cells through down-regulation of the X-linked inhibitor of apoptosis protein which could improve the effects of cytotoxic chemotherapy. Against this rationale, the experimental evidence is limited. No study designed to evaluate praziquantel in a breast cancer model was identified. The syntheses that studied the praziquantel chemosensitising effect in combination with paclitaxel did not show direct antineoplastic activity as monotherapy; a single recent paper reported a monotherapy effect of praziquantel on hepatoma lines, but this has not been tested in breast cancer. A substantial exposure gap separates the concentrations at which activity is reported *in vitro* from those achievable clinically, given a systemic bioavailability below 20 per cent, a plasma half-life of one to three hours and approximately 80 per cent albumin binding. The favourable tolerability record derives from single-dose mass administration rather than chronic dosing alongside cytotoxic therapy.

Conclusion: We conclude that praziquantel is at present a hypothesis rather than a candidate in breast oncology, and we set out the specific studies that would be required to change that assessment.

Keywords: Praziquantel, drug repurposing, breast neoplasms, 5-HT2B receptor, transient receptor potential channels, chemosensitisation, paclitaxel.

1. INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy in women and the leading cause of cancer death in that population. Estimates from the Global Cancer Observatory place the 2022 burden at approximately 2.3 million new cases and 666,103 deaths worldwide, with mortality-to-incidence ratios that differ sharply between high- and low-resource settings, reflecting inequities in early detection and access to systemic therapy [1]. Breast cancer is not a single disease but a molecularly heterogeneous group of tumours, where different subtypes have been

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discovered: Luminal A, Luminal B, HER2-enriched, Basal-like and Claudin-low. This differentiation may affect the drug response for each subtype [27]. This heterogeneity is crucial for any drug repurposing rationale, as the receptor-driven pathways such as TRP channels and 5-HT2B might differ across molecular subtypes. Even where modern endocrine therapy, anti-HER2 agents, cyclin-dependent kinase inhibitors and antibody-drug conjugates are available, advanced disease remains largely incurable, and the triple-negative subtype continues to lack a targetable receptor and to relapse early [2].

The result is a persistent demand for therapeutic options that are effective, tolerable and, critically, for the settings that carry the highest mortality-to-incidence ratios, affordable.

Conventional drug development answers that demand slowly. Attrition in late-phase trials is high, timelines run to a decade or more, and the resulting agents are frequently priced beyond the reach of the health systems that need them most. Drug repurposing offers a structurally different proposition: an approved medicine already carries a defined safety profile, a characterised pharmacokinetic behaviour, an established manufacturing route and, often, patent-expired pricing, so that the development question narrows from "is this molecule tolerable in humans" to "does it do anything useful in this disease" [3,4]. Among non-oncological drug classes examined in this way, the anthelmintics have attracted sustained interest. Benzimidazoles, salicylanilides, macrocyclic lactones and quinolines have all been reported to interfere with pathways relevant to tumour progression, and several have advanced to early-phase oncological evaluation [5,24].

Praziquantel occupies an unusual position within this class. It is the World Health Organization's recommended treatment for all forms of human schistosomiasis and has been administered to hundreds of millions of people through preventive chemotherapy programmes, giving it one of the largest real-world safety denominators of any medicine in the modern pharmacopoeia [7,8]. It is inexpensive, orally administered and off-patent. Interest in its antineoplastic potential has been reinforced by the discovery, over the past several years, of the molecular identity of its parasite target and of its off-target activity at human receptors, both of which intersect with pathways of established relevance to breast tumour biology [7,9-11].

That intersection has generated an appreciable secondary literature, in which praziquantel is routinely listed among anthelmintics with anticancer promise [5,24]. However, available syntheses list praziquantel as one item within the broader anthelmintic drug class without focusing specifically on it. These studies do not examine the breast-specific evidence base, the pharmacokinetic feasibility of achieving effective concentrations clinically, or the implications of enantiomer-specific pharmacology and these are the gaps this review addresses.

The purpose of this review is to examine whether the primary evidence supports that listing, specifically in relation to breast neoplasia. We set out the pharmacological rationale in detail, appraise the experimental data on its own terms, quantify the pharmacokinetic distance between laboratory and clinic, and identify the studies that would be needed before praziquantel could reasonably be described as a breast cancer candidate rather than a hypothesis.

2. APPROACH TO THE LITERATURE

This is a narrative review and does not follow a systematic review protocol. The search was done in June 2026 across PubMed/MEDLINE, Scopus, Web of Science and Google Scholar with combinations of the terms praziquantel, drug repurposing, drug repositioning, anthelmintic, cancer, neoplasm, carcinoma, breast, apoptosis, 5-HT2B, transient receptor potential and chemosensitisation. Records were limited to peer-reviewed articles published in English; conference abstracts, preprints, and non-peer-reviewed sources were excluded. Reference lists of retrieved articles were examined for further sources. Titles and abstracts were screened by two authors for relevance to praziquantel's mechanistic, pharmaco-kinetic, or antineoplastic profile; disagreements were resolved by discussion with a third author. Priority was given to work published from 2020 onwards, reflecting both the recency of the mechanistic advances that motivate current interest and the editorial preference for a contemporary evidence base. Readers should note one consequence of that restriction: several formative observations in this field were first reported before 2020 and are cited here through the recent syntheses that summarize them rather than through the original reports. Where that is the case, it is stated explicitly in the text. The lone exception to this rule is Wu *et al*. (2012), the original primary study explaining the praziquantel–paclitaxel synergy and XIAP mecha-nism. The study is cited directly, instead of only through

the secondary syntheses that summarize it, given its importance to the evidentiary basis of this review.

3. PRAZIQUANTEL: THE PHARMACOLOGY THAT MATTERS FOR ONCOLOGICAL REPURPOSING

3.1. Clinical Profile and Antiparasitic Mechanism

Praziquantel is a pyrazinoisoquinoline administered as a racemate, conventionally at a single oral dose of 40 mg/kg for schistosomiasis. Its antiparasitic action has long been attributed to a rapid increase in tegumental calcium permeability, producing sustained muscular contraction, tegumental damage and detachment of the worm from the mesenteric or vesical vasculature, after which it is cleared by host immune mechanisms [7]. The molecular basis of that effect remained undefined for most of the drug's clinical life. Two convergent lines of work resolved it, identifying a transient receptor potential channel of the melastatin subfamily, designated TRPM-PZQ, as the schistosome target: pharmacological characterisation demonstrated that praziquantel activates the channel to depolarize excitable cells in the parasite [9], while genetic analysis of variation in praziquantel response independently implicated the same channel family [10]. Antischistosomal activity resides principally in the R-enantiomer; the S-enantiomer contributes little efficacy and is generally held responsible for the preparation's unpalatability [12]. This enantiomer-specific pharmacology has direct implications for interpreting the antineoplastic evidence discussed in Sections 4 and 5, since preclinical work using racemic praziquantel cannot, on its own, attribute an observed effect to either enantiomer (see Section 6.2 for further discussion)

3.2. Human off-Target Pharmacology

The search for praziquantel's target also examined host proteins, on the reasoning that a molecule with such consistent clinical behaviour was unlikely to be pharmacologically silent in the human recipient. That work identified the human 5-hydroxytryptamine 2B receptor as a host target of the R-enantiomer, which behaves as a partial agonist with micromolar potency and with selectivity for 5-HT2B over the closely related 5-HT2A and 5-HT2C subtypes [7,11]. Subsequent mutagenesis and docking work defined the structural basis of that selectivity, localizing it to residues in transmembrane helices 5 and 6 and extracellular loop 2 of the orthosteric site, and established that receptor engagement is sufficient to constrict mesenteric vasculature in the treated host [11].

Two features of this pharmacology are relevant to any oncological proposal. First, the potencies involved are micromolar rather than nanomolar, which is consistent with the drug's benign side-effect profile at antiparasitic doses but sets a demanding exposure requirement for any therapeutic application that depends on host-receptor engagement. Second, and more consequentially, the direction of the pharmacological effect is agonist rather than antagonist at 5-HT2B, which has implications discussed in section 4.2.

3.3. Pharmacokinetics

Praziquantel is well absorbed but heavily metabolized on first pass, with the consequence that systemic bioavailability is below 20 per cent. It is hydroxylated principally to 4-hydroxypraziquantel and a range of further mono-, di- and tri-hydroxylated metabolites and conjugates, with CYP3A4, CYP1A2, CYP2C9 and CYP2C19 identified as the principal enzymes involved. The plasma half-life is between one and three hours and more than 80 per cent of an administered dose is excreted within 24 hours, with less than 0.02 per cent recovered as unchanged drug in urine, so that elimination is essentially wholly metabolism-dependent [12]. Approximately 80 per cent of circulating drug is albumin-bound, making the free fraction sensitive to nutritional status and inflammatory state.

Metabolism is markedly enantioselective. Using *in vitro* to *in vivo* extrapolation, CYP3A4 was estimated to contribute 89.88 per cent of S-praziquantel clearance, and reanalysis of a human interaction study confirmed this asymmetry: ketoconazole increased the area under the curve of the S-enantiomer by 68 per cent but that of the R-enantiomer by only 9 per cent [12]. Interindividual variability in exposure is correspondingly wide, a point emphasised in a dedicated review of praziquantel disposition across human and experimental settings [13]. For a repurposing programme these are not incidental details: they determine whether a target concentration can be reached at all, and whether the racemate is even the correct entity to be testing.

3.4. Tolerability

Praziquantel's safety record is genuinely favourable and is the strongest single argument in its favour as a repurposing candidate. Adverse events in mass drug administration are predominantly gastrointestinal and neurological, are mild to moderate, are usually transient within 24 hours, and are related to pre-

treatment infection intensity, consistent with an origin in the host response to dying parasites rather than in drug toxicity per se. Active safety surveillance in Ethiopian schoolchildren receiving praziquantel with albendazole reported this pattern, alongside cure rates of 89.1 per cent at week four and 87.5 per cent at week eight [14]; the World Health Organization guideline rates the overall certainty of evidence for praziquantel safety in at-risk populations as moderate, with persistent moderate or severe events uncommon [8].

This record should nonetheless be interpreted for what it is. It derives from single doses or short courses, administered to individuals who are for the most part otherwise well, and in whom follow-up rarely extends beyond a few weeks. It does not speak to the tolerability of continuous or repeated high-dose administration in patients concurrently receiving myelosuppressive cytotoxic therapy, which is the setting any breast oncology application would require. Extrapolating from the former to the latter is a common error in the repurposing literature and should be resisted.

4. MECHANISTIC RATIONALE FOR ACTIVITY IN BREAST NEOPLASIA

4.1. Calcium Signalling and the Transient Receptor Potential Channel Family

Dysregulated calcium handling is a recognised feature of breast tumour biology, and the transient receptor potential superfamily has emerged as a principal mediator. Members of the canonical, vanilloid and melastatin subfamilies are differentially expressed across breast cancer subtypes and contribute to proliferation, migration, invasion, apoptosis evasion and chemoresistance, with their protein-protein interaction networks proposed as a therapeutic target in their own right [2]. Within the melastatin subfamily, TRPM7 overexpression is associated with poor prognosis in breast cancer and with oncogenic signalling in preclinical models [16], while TRPM8 has been implicated across a range of malignancies including breast, where it is reported to influence proliferation and migration and has been proposed as both prognostic marker and pharmacological target [15].

TRP channels react differently across breast cancer molecular subtypes. For example, TRPC1 overexpression is linked with poor prognosis specifically in claudin-low/basal-like tumours, while TRPM4 is overexpressed across both ER+/PR+ and triple-negative subtypes [2]. TRPM7 overexpression is associated with poor prognosis in breast cancer generally; prognostic data have not been systematically stratified by molecular subtype, though the paucity of actionable therapeutic targets in triple-negative disease has prompted particular interest in TRPM7 as a target in this subtype [16]. The expression of TRPM8 in the cell increases with estrogen stimulation, which explains its higher presence in ER-positive tumours. However, the channel's role in invasion has been demonstrated in the triple-negative MDA-MB-231 cell line, which is ER-negative showing a clear separation between where the channel is expressed and where it actually drives aggressive behaviour.

The relevance to praziquantel is structural and pharmacological rather than direct. The drug's parasite target is itself a melastatin-subfamily transient receptor potential channel [9,10], and the deorphanisation work that identified it proceeded in part by screening host channel families. It is therefore a reasonable hypothesis that praziquantel engages one or more human transient receptor potential channels at concentrations relevant to its clinical use, and that such engagement could perturb calcium-dependent processes in mammary carcinoma cells. It must be stated plainly that this is a hypothesis. We identified no study that has tested praziquantel against human transient receptor potential channels in a breast cancer model, nor any that has established which, if any, human channel mediates a praziquantel effect on tumour cell behaviour. The inference from parasite target to human tumour target is at present an inference only.

4.2. Serotonergic Signalling: A Rationale that Cuts Both Ways

The 5-HT2B interaction is the best-characterised host pharmacology of praziquantel and, on its face, the most promising point of contact with breast tumour biology. Serotonergic signalling is active in multiple malignancies, where 5-HT receptors mediate mitogenic and pro-angiogenic effects, modulate apoptotic thresholds and shape antitumor immunity [17]. In breast tissue specifically, serotonin promotes proliferation of neoplastic mammary cells, and 5-HT2B expression in breast tumours correlates significantly with estrogen receptor-α expression, suggesting a possible enrichment in hormone receptor-positive disease; however, no correlation between 5-HT receptor subtype expression and tumour grade was identified, and subtype-specific expression data across the Luminal, HER2-enriched, and triple-negative molecular subtypes remain unavailable [17].

It is precisely this literature that generates the central concern of this review. If 5-HT2B signalling in breast tumours is predominantly tumour-promoting, then a partial agonist at that receptor is, on first principles, moving the system in the wrong direction. The relevant model work reinforces the concern rather than dispelling it: in colitis-associated cancer, 5-HT2B activation in enterocytes suppressed tumour initiation but promoted subsequent progression, establishing that the receptor's effect is stage-dependent and that the same intervention can be protective at one point in the natural history and harmful at another [18]. A drug that engages this receptor could therefore plausibly retard early transformation while accelerating established disease, which is close to the least desirable profile an adjuvant agent could have. This stage- and context-dependence is not an isolated observation confined to a single model system. A recent study attributes such contradictory roles of serotonin to three factors: first, tissue-specific receptor expression patterns; second, dose-dependent effects of ligand concentration; and third, the stage of tumour development [25]. HTR2B, the same receptor engaged by praziquantel has been shown to exert a dual, microenvironment-dependent role in colorectal cancer. The population of HTR2B-expressing cells increases under unfavourable conditions such as chemotherapy exposure, fibroblast co-culture, and extracellular matrix remodelling [26]. This is therefore a recognised and recurring pattern in 5-HT2B pharmacology more broadly, not an isolated finding confined only to the colitis model discussed above.

Against this, the one recent study to examine praziquantel monotherapy in a solid tumour model reported the opposite direction of effect. In Hep3B and Hepa1-6 hepatoma lines, praziquantel treatment increased 5-HT2B messenger RNA expression while reducing proliferation to 71.00 (SD 6.08) and 67.33 (SD 7.57) per cent at 72 hours, reducing migration, and increasing apoptosis to 16.13 (SD 0.66) and 20.70 (SD 2.85) per cent, with Bax increased and Bcl-2 decreased. Critically, co-treatment with the 5-HT2B antagonist RS127445 attenuated each of these effects, which the authors interpret as evidence that the antineoplastic action is receptor-mediated [19]. Two readings of that result are available. The first is that partial agonism at a receptor already subject to substantial tonic serotonergic tone can behave as functional antagonism, displacing a fuller agonist and lowering net signalling. The second is that the relationship between 5-HT2B occupancy and tumour cell behaviour is tissue-specific, and that a hepatic result carries limited predictive weight for mammary tissue. Neither reading can currently be excluded, and the choice between them is exactly the question that a breast-specific receptor pharmacology study would resolve. Until it is resolved, the serotonergic rationale should be presented as a question rather than as an argument in favour.

4.3. Apoptotic Priming through XIAP

The most reproducible mechanistic account of praziquantel's proposed as antineoplastic activity concerns the X-linked inhibitor of apoptosis protein. This protein is a potent endogenous inhibitor of caspase activity and a recognised contributor to chemoresistance. Recent syntheses of the anthelmintic repurposing literature report that praziquantel, at concentrations of 20 to 40 micromolar, increases the cytotoxicity of paclitaxel across several carcinoma lines, that the combination produces synergistic inhibition of growth and viability with mitotic arrest and caspase activation, and that down-regulation of the X-linked inhibitor of apoptosis protein is required for the interaction rather than merely associated with it [5,24]. This mechanism has an attractive property for breast oncology: it does not require praziquantel to be cytotoxic in its own right, only that it lower the threshold at which a partner agent becomes effective.

4.4. Immunomodulation

A further rationale, less developed but not negligible, concerns immune modulation. Anthelmintics as a class have been reviewed as emerging immune modulators in cancer, with reported effects on innate signalling, dendritic cell function and the composition of the tumour microenvironment [6]. Praziquantel is administered in a disease context defined by chronic helminth-driven type 2 immune skewing, and the immunological consequences of clearing that stimulus are appreciable. Whether any of this translates into an antitumor immune effect in a non-infected host is entirely untested, and we note it here as a direction rather than as evidence.

5. THE EXPERIMENTAL EVIDENCE BASE

5.1. Monotherapy Activity

The single most important observation for anyone considering praziquantel in breast cancer is that its reported antineoplastic activity is, with one recent exception, confined to combination settings. The syntheses that summarize this literature describe

praziquantel's contribution exclusively in terms of potentiating a partner cytotoxic agent and report no monotherapy signal in the carcinoma lines examined, which included breast, lung, cervical and colorectal models [5,24]. This is not a subtle qualification. It means that praziquantel is not, on current evidence, an anticancer drug in the ordinary sense, and that the framing sometimes encountered in the secondary literature, in which it appears in lists of agents with demonstrated antitumor activity, overstates what has been shown.

The exception is the hepatoma work described in section 4.2, which reports genuine single-agent effects on proliferation, migration and apoptosis [19]. That study is recent, is receptor-mechanistically anchored, and deserves to be taken seriously; it is also a single report, in two hepatic lines, without *in vivo* confirmation, and published in a specialist parasitology journal rather than an oncology venue. It shifts the question but does not settle it.

5.2. Chemosensitisation

The combination data are a substantive part of the case. Praziquantel has been reported to act synergistically with paclitaxel, producing mitotic arrest, activation of the apoptotic cascade and, in a murine xenograft, greater tumour growth inhibition than either agent alone, with X-linked inhibitor of apoptosis protein down-regulation as the required mechanism [5,24]. The relevance to breast oncology is immediate and specific: taxanes are a backbone of both neoadjuvant and metastatic breast cancer therapy, and taxane resistance is a defining clinical problem, particularly in triple-negative disease. An inexpensive, well-tolerated oral agent that restored taxane sensitivity would be of real value.

This case is nonetheless substantially weaker than the preceding paragraph might suggest, and the most consequential qualification should be stated first rather than last. The synergy was characterised principally in colorectal and lung carcinoma lines; no study has tested whether the same interaction — praziquantel-driven XIAP down-regulation potentiating paclitaxel — occurs in breast carcinoma cells at all. Extrapolating a two-drug interaction from colorectal and lung lineages to breast is not a safe default: XIAP expression, baseline apoptotic threshold, and taxane-response pathways all differ appreciably by tissue of origin and, within breast cancer itself, by molecular subtype. Establishing whether this synergy generalises to breast lines — and, if so, in which subtypes — is accordingly listed as the third most urgent experiment in the research agenda (Section 8, item 3). Two further qualifications compound this uncertainty: the effective concentration range of 20 to 40 micromolar sits at the upper end of what is achievable clinically, for reasons developed in Section 6; and the finding has not, to our knowledge, been independently replicated even in the

Table 1: Reported Preclinical Activity of Praziquantel in Malignant Models

Model / setting	Praziquantel exposure	Principal reported findings	Source
Panel of human carcinoma lines (lung, breast, cervical, colon), monotherapy	Up to 100 micromolar	No monotherapy signal reported; syntheses of this literature describe activity only in combination settings	[5,24]
DLD-1 colorectal carcinoma and further lines, combination with paclitaxel; murine xenograft	20-40 micromolar *in vitro*	Synergistic inhibition of growth and viability; mitotic arrest; caspase activation; down-regulation of XIAP required for synergy; enhanced tumour growth inhibition *in vivo* versus either agent alone	[5,24]
Hep3B (human) and Hepa1-6 (murine) hepatoma lines, monotherapy	30 µg/mL (approximately 96 micromolar)	Up-regulation of 5-HT2B mRNA; proliferation reduced to 71.00 (SD 6.08) and 67.33 (SD 7.57) per cent at 72 h; migration reduced; apoptosis increased to 16.13 (SD 0.66) and 20.70 (SD 2.85) per cent; Bax increased, Bcl-2 decreased; effects attenuated by the 5-HT2B antagonist RS127445	[19]
Dedicated breast carcinoma model (*in vitro*, *in vivo* or clinical)	Not applicable	No study identified that was designed to evaluate praziquantel in breast neoplasia; the only breast lines appearing in this literature do so within multi-lineage screening panels	--

SD, standard deviation; XIAP, X-linked inhibitor of apoptosis protein.

original lineages in the intervening period. A mechanism that has been described once and cited many times is different from a mechanism that has been reproduced — and a mechanism reproduced in one tissue is not the same as a mechanism demonstrated in the tissue under discussion.

5.3. Breast-Specific Evidence

We identified no study designed to evaluate praziquantel in breast neoplasia. Breast carcinoma lines appear in this literature only as members of multi-lineage screening panels, and in that context contributed to the negative monotherapy finding rather than to any positive signal. There is no reported work in patient-derived breast models, no orthotopic or spontaneous mammary tumour model, no evaluation against the molecular subtypes that determine breast cancer treatment, and no clinical data of any kind. Table **1** summarizes the evidence base in full.

This absence is worth stating without euphemism because the framing of a review determines how its conclusions are used. A reader encountering praziquantel in a list of anthelmintics with anticancer potential could reasonably infer that breast-relevant data exist. They do not.

6. TRANSLATIONAL BARRIERS

6.1. The Exposure Gap

The most substantial obstacle is arithmetic. Activity *in vitro* is reported in the range of 20 to 40 micromolar and, in a culture system, that concentration is maintained continuously for the duration of the experiment. Achieving a comparable free-drug exposure in a patient is a different proposition. Systemic bioavailability is below 20 per cent, the plasma half-life is one to three hours, more than 80 per cent of an administered dose is eliminated within 24 hours, and approximately 80 per cent of what does circulate is albumin-bound, so that the pharmacologically available fraction is a fifth of the measured total [12,13]. A conventional antischistosomal dose therefore produces a brief, low-micromolar total-drug excursion, not a sustained one, and the free concentration is lower still.

This qualitative picture can be given an approximate quantitative anchor. In a pharmacokinetic study using a 20 mg/kg oral dose in healthy volunteers, mean peak plasma concentrations of 313 ng/mL (R-praziquantel) and 783 ng/mL (S-praziquantel) were reported, summing to approximately 3.5 micromolar total racemic drug [12]. Applying the unbound fraction of 0.2 used in the same pharmacokinetic analysis [12] yields an estimated peak free concentration of approximately 0.7 micromolar; scaling linearly to the standard 40 mg/kg antischistosomal dose — an approximation that assumes dose-proportional pharmacokinetics, which has not been formally established for praziquantel — gives an estimated peak free concentration on the order of 1 to 1.5 micromolar. Set against this, achievable free-drug exposure sits roughly one to two orders of magnitude below the 20 to 40 micromolar range characterising the paclitaxel-sensitisation studies, and further still below the approximately 96 micromolar concentration used in the sole monotherapy report (Section 5.1). This calculation is illustrative rather than definitive: it rests on a single-dose Cmax rather than a formal population pharmacokinetic model, assumes linear dose-scaling, and does not account for interindividual variability, food effects, or the enantiomer-specific clearance discussed in Section 6.2. A population pharmacokinetic analysis incorporating unbound-drug measurement would be required to establish this gap with confidence.

This gap is not necessarily fatal, but it cannot be ignored, and it is ignored with some regularity in the repurposing literature. Any serious programme would need either a formulation strategy capable of sustaining exposure, a delivery approach that concentrates drug at the tumour, or a demonstration that intermittent high-peak exposure timed to the chemotherapy window is sufficient for a chemosensitising effect. The last of these is the most tractable and, notably, has not been tested.

6.2. Which Molecule is being Tested

Praziquantel is a racemate whose enantiomers differ in target engagement, in potency and in clearance. The R-enantiomer carries the antischistosomal activity and the 5-HT2B pharmacology; the S-enantiomer is metabolized overwhelmingly by CYP3A4 and dominates the exposure profile after racemic dosing [12]. Preclinical antineoplastic work using the racemate therefore reports the aggregate behaviour of two pharmacologically distinct molecules present in unequal and variable proportions and cannot attribute an observed effect to either. Given that enantiopure R-praziquantel formulations have been under development for antiparasitic indications, there is no methodological reason for oncological work to continue using the racemate.

6.3. Interaction Liability in an Oncology Population

Praziquantel's dependence on CYP3A4 for elimination makes it vulnerable to interaction in exactly the population where it would be used. Clinically relevant, enantiomer-specific pharmacokinetic interactions with CYP3A4 perpetrators have been documented [20], and the ketoconazole data cited above show that inhibition can raise S-enantiomer exposure by more than two-thirds while barely affecting the R-enantiomer [12]. Patients receiving breast cancer therapy are commonly exposed to azole antifungals, certain antiemetics, corticosteroids and targeted agents that modulate this enzyme, and the direction of the resulting change would differ between the two enantiomers. Any combination proposal would require formal interaction characterisation against the intended backbone before, not after, efficacy testing.

6.4. Safety Data that do Not Extend to the Intended Use

As discussed in section 3.4, the tolerability evidence concerns single-dose or short-course administration in ambulatory, largely healthy populations [8,14]. Repeat-dose toxicology adequate to support continuous administration alongside cytotoxic chemotherapy has not been published, and hepatic exposure in particular warrants attention given the extent of first-pass metabolism and the concurrent hepatotoxic potential of several breast cancer regimens. Table **2** summarizes the barriers and the corresponding mitigation strategies.

7. A STRONGER ADJACENT CASE: PREVENTION RATHER THAN TREATMENT

A distinction should be drawn between praziquantel as an antineoplastic agent and praziquantel as an instrument of cancer prevention, because the evidence for the two propositions is of entirely different quality. Schistosoma haematobium is a recognised human carcinogen strongly associated with bladder squamous cell carcinoma, and its eradication through praziquantel treatment is a coherent, causally grounded preventive measure [21,22]. That is a materially different argument from the proposition that praziquantel has intrinsic activity against an established tumour, and it does not extend to breast neoplasia, for which no comparable

Table 2: Principal Translational Barriers to Praziquantel Repurposing in Breast Oncology and Possible Mitigation

Barrier	Underlying evidence	Possible mitigation
Exposure gap	Reported *in vitro* chemosensitising range is 20-40 micromolar and sustained, whereas systemic bioavailability of praziquantel is below 20 per cent, plasma half-life is 1-3 h and more than 80 per cent of a dose is eliminated within 24 h	Enantiopure or modified-release formulations; nanocarrier delivery; loco-regional administration; front-loaded schedules timed to the chemotherapy window
Plasma protein binding	Praziquantel is approximately 80 per cent albumin-bound, so free drug is a fraction of measured total concentration and varies with nutritional and inflammatory status	Report unbound rather than total concentrations; account for the albumin content of culture medium when translating *in vitro* potency
Enantiomer-specific pharmacology	The two enantiomers differ in target engagement and in clearance; CYP3A4 contributes an estimated 89.88 per cent of S-praziquantel metabolism, and ketoconazole raises S-praziquantel exposure by 68 per cent versus 9 per cent for the R-enantiomer	Test enantiomers separately rather than the racemate; specify which enantiomer any observed antineoplastic effect is attributed to
Drug-drug interaction liability	Clinically relevant, enantiomer-specific pharmacokinetic interactions with CYP3A4 perpetrators are documented	Formal interaction studies against the intended chemotherapy backbone before any combination trial
Target-directionality uncertainty	The R-enantiomer is a partial agonist at 5-HT2B, a receptor whose signalling is context-dependent and, in several settings, tumour-promoting	Receptor-level pharmacology in breast models before efficacy work; include angiogenesis and metastasis endpoints, not proliferation alone
Absence of chronic-dosing safety data	The favourable safety record derives from single-dose and short-course mass administration, not from continuous exposure in patients receiving cytotoxic therapy	Dedicated repeat-dose toxicology and early-phase safety work in an oncology population

CYP, cytochrome P450.

infectious aetiology has been established. Reviews that move between these two claims without marking the transition risk conferring on the weaker proposition the credibility earned by the stronger one.

8. A RESEARCH AGENDA

If the question of praziquantel's utility in breast cancer is to be resolved rather than perpetuated, the following studies would be required. Rather than a single strict sequence, they fall into three categories of priority: item 1 is the true gatekeeping experiment — a negative result there would substantially undermine the case for continuing, and it should be completed before further resources are committed. Item 2 is a cross-cutting methodological standard that should govern every subsequent experiment listed below, rather than a discrete study in its own right. Items 3, 4 and 6 can proceed in parallel once item 1 is positive; item 5 is explicitly downstream of all preceding items; and item 7 is a contingency, to be pursued only if the pharmacokinetic barriers discussed in item 4 and Section 6 prove intractable.

1. **Determine the direction of the receptor effect in breast tissue.** Characterise 5-HT2B expression and signalling in a panel of breast carcinoma lines representing the major molecular subtypes and establish whether R-praziquantel behaves as a functional agonist or antagonist in that context. This is the single study most likely to determine whether the programme is worth pursuing, and it should precede any efficacy work. Endpoints should include angiogenic and migratory readouts, not proliferation alone, given the stage-dependent effects reported for this receptor [18].

2. **Test enantiomers separately.** All subsequent work should use enantiopure R- and S-praziquantel rather than the racemate and should report which enantiomer any effect is attributed to [12].

3. **Replicate the chemosensitisation finding in breast models.** Formal combination-index analysis of praziquantel with paclitaxel and with docetaxel in taxane-sensitive and taxane-resistant breast lines, with X-linked inhibitor of apoptosis protein as the mechanistic readout, would establish whether the reported synergy generalizes to the lineage in which taxanes are most used [5,24].

4. **Anchor concentrations to achievable exposure.** *In vitro* work should report unbound rather than total concentrations, should account for the albumin content of the culture medium, and should include at least one arm modelling the intermittent, short-duration exposure profile that oral dosing actually produces rather than continuous incubation alone [12,13].

5. **Progress to orthotopic and patient-derived models only if the above are positive.** Subcutaneous xenografts of non-breast lineage have limited predictive value for breast cancer; orthotopic mammary models and patient-derived xenografts, with pharmacokinetic sampling to confirm that target exposure was achieved, would be the appropriate next step.

6. **Characterise interactions before proposing combinations.** Formal evaluation of praziquantel against CYP3A4 perpetrators commonly co-administered in breast oncology, and against the intended chemotherapy backbone [20].

7. **Consider chemical optimization as an alternative to repurposing the parent molecule.** If the pharmacophore is of interest but the pharmacokinetics are prohibitive, analogue and hybrid synthesis around the praziquantel scaffold is an established approach and may deliver a molecule with the required exposure profile more readily than reformulation of the parent drug [23].

9. CONCLUSION

Evidence in Favour

Praziquantel has several of the properties that make a repurposing candidate attractive: it is inexpensive, orally administered, off-patent, extensively characterised and exceptionally well tolerated at the doses in current use. It also has a mechanistic rationale that is more specific than most, resting on a defined interaction with the human 5-HT2B receptor and on a parasite target belonging to a channel family whose human members have established roles in breast tumour biology, raising an untested hypothesis about praziquantel's engagement with the human channels specifically.

Principal Gaps

What it does not have is evidence. No study has been designed to evaluate praziquantel in breast neoplasia. The antineoplastic activity attributed to it in

the secondary literature is, on the primary evidence summarised in recent syntheses, confined to potentiation of paclitaxel, characterised chiefly in non-breast models, at concentrations that sit uncomfortably close to the ceiling of what oral dosing can achieve. The one recent monotherapy report concerns hepatoma lines and awaits replication. The receptor pharmacology that constitutes the most specific part of the rationale points, on current understanding of serotonergic signalling in breast tissue, in a direction that is at best ambiguous and at worst counterproductive.

Conditions for Further Development

The appropriate conclusion is therefore neither dismissal nor endorsement. Praziquantel in breast cancer is a hypothesis with a defensible mechanistic basis and an unusually favourable development profile should the hypothesis prove correct. It is not yet a candidate. The distinction matters because the resources available for repurposing research are finite and are best directed by an accurate reading of what has and has not been shown. The studies set out in section 8 would provide that reading; in their absence, claims for praziquantel's antineoplastic utility in breast cancer should be regarded as premature.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization: **F.M.O. and M.I.** Methodology, including the design of the search strategy and source-selection criteria: **F.M.O., W.A., T.M.A., and M.I.** Investigation, comprising the literature search, screening of retrieved records, and appraisal of included sources: **F.M.O., W.A., J.G.J., N.B.S.A., N.O.Y.E., and T.Y.E.** Data curation and preparation of Tables **1** and **2**: **F.M.O., W.A., J.G.J., N.B.S.A., N.O.Y.E., and T.Y.E.** Writing – original draft: **F.M.O., W.A., T.M.A., J.G.J., N.B.S.A., N.O.Y.E., and T.Y.E.** Writing – review and editing: **F.M.O., W.A., T.M.A., J.G.J., N.B.S.A., N.O.Y.E., T.Y.E., and M.I.** Critical revision of the manuscript for important intellectual content: **T.M.A. and M.I.** Supervision and project administration: **M.I.** All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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DATA AVAILABILITY

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. This article is a narrative review of previously published literature and did not involve human participants, human tissue, identifiable personal data or animal subjects; ethical approval and informed consent were therefore not required.

CONSENT FOR PUBLICATION

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