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Current Status of Opisthorchiasis Therapy: Praziquantel and Plant-derived compounds

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ABSTRACT

This lecture examines contemporary therapeutic strategies for opisthorchiasis, focusing on infections caused by the liver fluke *Opisthorchis felineus*, endemic in Western Siberia. While praziquantel remains the first-line treatment, its clinical utility is constrained by several factors, including lack of efficacy against juvenile parasite forms and emerging drug resistance. The discussion explores alternative pharmacological approaches, encompassing novel synthetic agents, combination therapies, and compounds targeting parasite-specific metabolic pathways. Special attention is given to plant-derived bioactive substances with experimentally confirmed anti-opisthorchiasis activity, including curcumin, *Thunbergia laurifolia* and *Allium sativum* extracts, and xanthohumol. These phytochemicals demonstrate dual therapeutic potential: direct antiparasitic effects and modulation of infection-associated pathophysiological processes, such as oxidative/nitrosative stress attenuation, inflammatory response suppression, and hepatobiliary fibrosis progression delay. A synergistic treatment paradigm combining praziquantel's anthelmintic properties with the pleiotropic effects of plant-based antioxidants and anti-inflammatory compounds shows particular promise. This strategy may improve parasite clearance rates, reduce treatment-related adverse events, and prevent chronic complications. Further investigation is warranted to refine combination protocols, develop targeted delivery systems, and identify next-generation anthelmintic compounds capable of addressing the limitations of current synthetic therapies.

Keywords: *Opisthorchis felineus*, anthelmintic therapy, praziquantel, combination therapy, antioxidants

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Современное состояние проблемы терапии описторхоза: празиквантел и соединения растительного происхождения

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РЕЗЮМЕ

Представлен обзор современных стратегий терапии описторхоза. Особое внимание уделяется инвазии печеночным сосальщиком *Opisthorchis felineus*, эндемичным на территории Западной Сибири. Несмотря на длительное применение празиквантела в качестве препарата первой линии, его использование сопряжено с рядом существенных ограничений, включая неэффективность против личиночных стадий и потенциальную резистентность у паразитов. Рассматриваются альтернативные подходы к лекарственной терапии с использованием синтетических препаратов, соединений комбинированного состава и агентов, направленных на специфические метаболические системы паразита. Отдельно приводится исчерпывающий обзор биологически активных веществ растительного происхождения, продемонстрировавших в экспериментах противоописторхозную активность (куркумин, экстракты *Thunbergia laurifolia* и *Allium sativum*, ксантогумол). Ценность этих соединений заключается не только в их потенциальных противопаразитарных свойствах, но и в способности модулировать ключевые патофизиологические процессы на фоне инвазии: подавлять окислительный и нитрозативный стресс, уменьшать выраженность воспалительных реакций и замедлять развитие фиброза гепатобилиарной системы. Наиболее обоснованной стратегией представляется комбинированная терапия, объединяющая противопаразитарное действие празиквантела с разнонаправленными эффектами растительных антиоксидантов и противовоспалительных агентов. Такой подход позволяет повысить эффективность эрадикации паразита, снизить нежелательные побочные эффекты антигельминтной терапии и минимизировать риск развития хронических осложнений инвазии. Подчеркивается необходимость дальнейших исследований для оптимизации комбинированных схем, разработки систем направленной доставки действующих веществ и поиска новых высокоактивных соединений для преодоления текущих ограничений синтетических антигельминтных лекарственных средств.

Ключевые слова: *Opisthorchis felineus*, антигельминтная терапия, празиквантел, комбинированная терапия, антиоксиданты

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INTRODUCTION

Liver diseases caused by parasitic trematodes, cestodes, and nematodes continue to pose a substantial global health threat [1]. Among these, trematode infections represent a distinct epidemiological challenge [2], with particular recent emphasis on species from the families *Schistosomatidae*, *Opisthorchiidae*, *Fasciolidae*, and *Paragonimidae* [3–5].

Opisthorchis felineus (*O. felineus*) stands as a principal causative agent of opisthorchiasis, capable of producing both asymptomatic infections and severe hepatobiliary pathology, including cholecystitis,

cholangitis, and periductal fibrosis. Chronic *O. felineus* infection is further associated with elevated risk of cholangiocarcinoma development [6–8]. Emerging evidence suggests that chronic *O. felineus* infection may modulate host immune responses, potentially exacerbating comorbid conditions [9]. This parasite remains the dominant etiological agent across extensive territories encompassing Russia, Kazakhstan, and several European nations [8, 10], with infection prevalence reaching peak levels in Western Siberia [8].

The well-documented endemic status of *O. felineus* in Western Siberia, supported by longitudinal surveillance data, highlights the urgent

need to strengthen epidemiological monitoring of transmission patterns, refine diagnostic algorithms, and optimize therapeutic protocols with consideration for regional characteristics and patient comorbidities.

Current research priorities demand systematic consolidation of existing knowledge regarding therapeutic interventions against *O. felineus*-induced opisthorchiasis, with specific focus on: the application of bioactive compounds; their incorporation into combination therapies with praziquantel (PZQ) – the current therapeutic mainstay; and the development of novel antiparasitic agents and treatment strategies to circumvent potential PZQ resistance in adult flukes while enhancing therapeutic efficacy [10, 11].

PRAZIQUANTEL – THE FIRST-LINE PHARMACOTHERAPEUTIC AGENT FOR OPISTHORCHIASIS

Pharmacotherapy remains the principal approach for targeted reduction of opisthorchiasis prevalence, with praziquantel (PZQ) – an isoquinoline derivative – standing as the sole anthelmintic of choice for trematode infections. For opisthorchiasis treatment, WHO recommends either: (1) a dosage regimen of 25 mg / kg PZQ administered three times daily for two to three days, or (2) a single 40 mg / kg dose [10]. However, clinical practice frequently employs an alternative protocol: an initial 50 mg / kg dose followed by 25 mg / kg on the subsequent day [10]. The therapeutic efficacy of PZQ may diminish with prolonged infection duration and higher parasitic load, necessitating repeat treatment courses. Given the compound's hepatotoxicity and other adverse events, such retreatment poses significant clinical concerns [11].

The anti-opisthorchiasis mechanism of PZQ involves selective disruption of Ca^{2+} homeostasis within the parasite. *In vitro* studies demonstrate that introducing PZQ into the culture medium containing adult flukes (maritae) induces intracellular Ca^{2+} accumulation through dissociation of slow calcium channel subunits in the liver fluke's muscular system, resulting in sustained muscle contraction and paralysis [12, 13]. Nevertheless, emerging evidence suggests that calcium channel modulation cannot fully explain PZQ's antiparasitic activity, as pre-incubation of trematodes with cytochalasin D (which lacks calcium transport effects) completely

inhibits PZQ efficacy [14]. Paradoxically, juvenile developmental stages exhibit measurable Ca^{2+} elevation upon incubation in PZQ-containing medium despite their well-documented drug resistance [14].

The tegument – a unique syncytial epithelial layer covering parasitic flatworms – may represent another pharmacological target. Current hypotheses propose that PZQ's mechanism includes direct tegumental damage, leading to parasite antigen exposure and subsequent host immune response activation [15]. An additional facet of PZQ's antiparasitic action involves nucleoside transport disruption (specifically adenosine and uridine) via transporter protein inhibition. This induces ATP depletion, reduced adenine/uridine nucleotide pools, and consequent metabolic dysfunction with impaired RNA/DNA synthesis [16].

It should be emphasized that commercial PZQ preparations contain a racemic mixture of isomers, with only the levorotatory isomer demonstrating antiparasitic activity [17].

Despite its high efficacy against trematodes, particularly *O. felineus*, PZQ administration faces several significant limitations. Considerable attention in specialized literature focuses on the pronounced cytotoxicity of PZQ's S-enantiomer [18]. However, the most critical issue – substantiated by multiple clinical observations in endemic regions – involves the potential development of PZQ resistance in trematodes [19]. *In vitro* studies confirm that adult helminths under continuous PZQ exposure develop increased pharmacological tolerance [20]. A particularly controversial yet crucial safety consideration involves the potential association between repeated PZQ courses and cholangiocarcinoma risk [19, 21]. This carcinogenic risk hypothesis stems from well-documented evidence of massive parasite antigen release within 24 hours post-PZQ administration, leading to antigen accumulation, induction of systemic inflammation in patients, and significant intensification of oxidative and nitrosative stress [19]. Conversely, some animal model studies described in separate sources suggest potential reduction of cholangiocarcinoma risk following repeated “infection–PZQ treatment” cycles [22].

Furthermore, PZQ demonstrates neither prophylactic activity nor efficacy against juvenile

parasite stages, representing a critical gap in developing mass chemoprevention strategies for high-incidence regions [23].

The cumulative evidence regarding PZQ's cytotoxicity, resistance development, and potential carcinogenic risk underscores the urgent need for novel therapeutic strategies and agents against opisthorchiasis. Promising candidates include synthetic benzimidazole derivatives (albendazole, mebendazole) and tribendimidine – compounds with fundamentally different molecular targets in the parasite. Particular interest lies in developing hybrid molecules that combine antiparasitic activity with improved safety profiles. As will be discussed below, these approaches offer a potential for overcoming PZQ's limitations while maintaining therapeutic efficacy against *O. felineus* and related trematodes.

ALTERNATIVE PHARMACOLOGICAL STRATEGIES FOR OPISTHORCHIASIS THERAPY USING SYNTHETIC COMPOUNDS

During the 1980s, *in vitro* and *in vivo* experiments, including clinical studies, were conducted to evaluate the specific anti-opisthorchiasis activity of albendazole and mebendazole [24]. Previously, these drugs were extensively used for treating soil-transmitted nematode infections [25].

Albendazole and mebendazole belong to the same drug class (benzimidazole derivatives) and exhibit broad-spectrum antiparasitic activity, including efficacy against nematodes, cestodes, and liver fluke infections [26, 27]. These agents disrupt microtubule function in parasitic cells by inhibiting β -tubulin polymerization into microtubules, subsequently leading to reduced glucose transport, glycogen depletion in *Opisthorchis*, impaired tegumental protein secretion, and neuromuscular transmission deficits [10, 26]. It should be noted that mebendazole acts as a direct active molecule against the parasite, whereas albendazole requires metabolic activation through transformation into a sulfoxide derivative [27]. Crucially, albendazole's pharmacologically active metabolite demonstrates greater affinity for parasitic β -tubulin compared to mebendazole, penetrates helminth tissues more effectively, and may additionally disrupt ATP synthesis. Indeed, the therapeutic regimen involving albendazole (10 mg / kg for 7 days) serves as an alternative to

conventional PZQ and is recommended by the US Centers for Disease Control and Prevention for liver fluke infections. Albendazole dosing regimens for *Clonorchis sinensis* infection – 8 mg / kg twice daily for 5 days and 10 mg / kg twice daily for 7 days – demonstrated 100% efficacy, while 5 mg/kg twice daily for 7 days achieved cure in 27 of 32 study participants [10].

However, albendazole administration (400 mg twice daily for 7 days) against *Opisthorchis viverrini* yielded only 33.3% efficacy (complete cure in 9 of 27 patients), despite a 95.0% reduction in egg output [28]. Low-dose albendazole (single 400 mg dose) and mebendazole (400 or 500 mg) showed minimal efficacy against both *C. sinensis* and *O. viverrini*. Another source evaluating albendazole's anti-opisthorchiasis activity reported moderate therapeutic efficacy with twice-daily 400 mg dosing for 3–4 days, despite >92% reduction in fecal egg counts [28]. Conversely, W. Sangkam et al. investigated mechanisms of albendazole, niclosamide, and mebendazole against *O. viverrini*, assessing oxidative stress intensity, worm motility, and tegumental morphology [29]. The authors demonstrated significant potential of these agents as alternative therapeutics for *O. viverrini* infection [29].

Particular interest merits efforts to develop combined pharmacological agents incorporating synthetic drugs alongside plant-derived bioactive compounds. Recently, a novel complex of albendazole with arabinogalactan polysaccharide – derived from *Larix sibirica* and *Larix gmelinii* wood – was synthesized, and its anthelmintic activity against *O. felineus* was evaluated [30]. The synthesized albendazole-arabinogalactan complex demonstrated high efficacy in suppressing liver fluke infection, exhibiting anthelmintic activity at doses tenfold lower than either constituent compound administered separately. Moreover, significant reductions in overall toxicity and selective hepatotropic adverse effects were documented for the complex compared to isolated administration of its components. The authors concluded that the albendazole-arabinogalactan complex represents a safer and more effective anti-opisthorchiasis agent than albendazole alone, thereby establishing a promising pathway for novel anthelmintic development [30].

Beyond strategies for enhancing classical anthelmintic efficacy through hybrid complex formation, an alternative approach involves employing original synthetic agents. The next stage in searching for PZQ alternatives focused on evaluating compounds with innovative chemical structures. Among these stands tribendimidine – a synthetic amidinophenylimidazole derivative.

Tribendimidine was approved by China's National Medical Products Administration for treating soil-transmitted helminthiasis and has also demonstrated high efficacy against liver fluke infections [31]. As with PZQ, tribendimidine's precise pharmacological mechanism remains incompletely understood. Current hypotheses suggest that increased lysophospholipid levels induced by this drug activate various helminth protein kinases – including tyrosine kinases, protein kinase C, and mitogen-activated protein kinases – leading to tegumental cell damage and host immune system recognition of parasite-specific antigens [32]. When administered as a single 400 mg dose to adults, tribendimidine achieved complete cure in 50% of *C. sinensis*-infected patients and 91.5% of *O. viverrini* cases [33, 34].

Moreover, the reduction rate of egg output in opisthorchiasis patients exceeded 99% [34]. Additional *in vivo* and *in vitro* experiments have demonstrated tribendimidine's potential efficacy specifically against *O. felineus* [11].

While the search for fundamentally new compounds (including tribendimidine) continues, PZQ remains the gold standard for opisthorchiasis pharmacotherapy. This undisputed status drives intensive research efforts to overcome its limitations through structural derivative development [35]. Studies by Novosibirsk researchers evaluated the efficacy of a supramolecular PZQ complex with disodium glycyrrhizinate against *O. felineus* infection in hamsters. *In vitro* experiments demonstrated that the “PZQ–disodium glycyrrhizinate” complex induced rapid parasite immobilization (1.5 times faster than PZQ alone) and caused significant tegumental damage [36, 37].

In vivo studies revealed the developed PZQ–disodium glycyrrhizinate complex surpassed standard PZQ in efficacy against *O. felineus*, attributable to both enhanced active substance (PZQ)

bioavailability and disodium glycyrrhizinate's pronounced anti-inflammatory effects.

However, numerous studies testing PZQ derivatives have failed to demonstrate superior efficacy compared to the parent molecule. The promising *in vitro* activity of potential PZQ derivatives often doesn't correlate with animal study results, as their pharmacokinetics and biotransformation profiles constitute key determinants of *in vivo* efficacy [38].

The aforementioned evidence underscores the necessity for developing novel pharmacological strategies for opisthorchiasis chemotherapy, focusing on identifying molecular targets within the parasite – particularly specific parasitic proteins or metabolic pathway components [39]. Beyond direct anthelmintic effects, targeting critical metabolic processes essential for parasite survival represents a promising direction. In this context, hemozoin – a crystalline heme detoxification product – holds particular interest, as its formation proves critical for blood-feeding trematodes. Hemozoin (β -hematin) formation constitutes a fundamental physiological process in *Opisthorchis*, enabling neutralization of toxic heme [40, 41].

Chloroquine, a classic antimalarial drug, exerts its primary effect by inhibiting heme biocrystallization into hemozoin. This leads to soluble heme accumulation, which generates reactive oxygen species, inducing oxidative stress and parasite death [42]. As early as 1955, chloroquine demonstrated moderate anti-opisthorchiasis activity in *O. viverrini*-infected patients [42]. Recent studies confirmed hemozoin crystal formation in *O. felineus* and *C. sinensis* trematodes, while being absent in the closely related *O. viverrini* [40, 41].

This observation likely accounts for the limited therapeutic efficacy of chloroquine observed in *O. viverrini*-infected patients. Importantly, when targeting the hemozoin-producing *O. felineus*, chloroquine exhibits significant potential for disrupting a vital metabolic pathway essential for parasite survival. The drug's inhibition of hemozoin biogenesis results in the accumulation of cytotoxic free heme, subsequent generation of reactive oxygen species, and ultimately parasite death – a mechanism analogous to its well-characterized action against both *Plasmodium spp.* and *Schistosoma* parasites. These findings highlight the compelling rationale

for investigating chloroquine's therapeutic potential against *O. felineus*-induced opisthorchiasis, particularly in endemic Siberian populations.

In a comprehensive screen of novel benzimidazole derivatives targeting adult *S. mansoni* in murine models, several compounds demonstrated remarkable anthelmintic efficacy (70 P.85%) comparable to PZQ. Notably, these compounds exhibited broad-spectrum activity against both mature and juvenile developmental stages. The study identifies a promising new class of potential antischistosomal agents, with mechanistic studies suggesting their activity stems from selective inhibition of hemozoin formation through specific β -hematin binding and subsequent disruption of crystallization processes [43].

The cytochrome P450 system of *O. felineus* represents another promising target for novel trematocidal agents. This enzyme exhibits high activity in opisthorchid tissues and plays a crucial role in parasite physiology [44, 45]. Published evidence indicates that inhibitors of heme-containing enzymes (particularly azole derivatives) suppress parasitic cytochrome P450 activity and significantly reduce *O. felineus* viability [44, 45]. Among azole derivatives demonstrating *in vitro* efficacy against *O. felineus* are the antifungal agents miconazole and clotrimazole [46]. However, the synergistic effects of PZQ-clotrimazole and PZQ-miconazole combinations observed *in vitro* failed to translate to *in vivo* models [47].

Thus, despite PZQ's dominant position in opisthorchiasis treatment, accumulated evidence reveals critical limitations: inefficacy against juvenile parasite stages, emerging resistance risks in endemic areas, and observed correlations with cholangiocarcinogenesis in certain studies. These findings have spurred the exploration of alternative synthetic agents. Research confirms moderate efficacy of benzimidazoles (albendazole, mebendazole), particularly during extended regimens, though their effectiveness varies by trematode species and dosing protocols. A significant breakthrough involves hybrid compound development, exemplified by the albendazole–arabinogalactan complex demonstrating enhanced anthelmintic activity with reduced hepatotoxicity compared to monotherapy. Tribendimidine, another promising candidate, shows high efficacy against *O. viverrini* with favorable

safety profiles. Parallel efforts focus on PZQ molecular modifications, including supramolecular complexes with disodium glycyrrhizinate to improve bioavailability and confer complementary anti-inflammatory effects. Investigations of parasitic enzyme inhibitors (particularly *O. felineus* cytochrome P450) reveal azole derivative potential, while chloroquine application (especially combined with PZQ) in *O. felineus*-endemic regions may theoretically provide synergistic action through dual targeting: disrupting calcium homeostasis (PZQ) and heme metabolism (chloroquine). The critical remaining challenge involves translating *in vitro* findings to clinical practice, hindered by complex pharmacokinetics and insufficient metabolic profiling of novel compounds.

These limitations of synthetic approaches – particularly their toxicity during repeated courses and unresolved inefficacy against juvenile forms – underscore the growing importance of investigating plant-derived bioactive compounds, which will be examined in detail in the following section. Their fundamental advantage lies in multicomponent action that combines direct anthelmintic activity with pathophysiologically grounded effects: oxidative stress suppression, inflammation mitigation, and fibrogenesis inhibition.

Moreover, as will be discussed subsequently, combinations of plant antioxidants with PZQ may unveil novel therapeutic prospects. Such formulations could simultaneously neutralize the adverse consequences of intoxication associated with oxidative stress and parasite antigen release, while potentially reducing risks of chronic infection complications.

PLANT-DERIVED BIOACTIVE COMPOUNDS AS PROMISING AGENTS FOR OPISTHORCHIASIS THERAPY

Modern parasitology is increasingly exploring the potential of natural biomolecules not only as sources of novel anthelmintic compounds, but also as modulators of invasion-related pathophysiological consequences. Research into plant-derived bioactive substances for opisthorchiasis treatment focuses on their capacity to complement and potentiate PZQ effects, mitigate its adverse reactions, and crucially – disrupt the cascade of events leading to chronic bile duct inflammation.

Recent years have witnessed the identification of several promising plant-derived bioactive compounds for developing novel anti-opisthorchiasis agents. It should be emphasized that the majority of these substances exhibit pronounced antioxidant activity. Regrettably, in contrast to schistosomiasis research, studies evaluating the anti-opisthorchiasis potential of antioxidant biomolecules remain relatively limited [24]. A notable exception is curcumin – a polyphenolic curcuminoid derived from *Curcuma longa* rhizomes – which has garnered particular research interest as a promising candidate for new anti-opisthorchiasis agents. Experimental evidence demonstrates that curcumin administration in *O. viverrini*-infected hamsters significantly reduces oxidative DNA damage while suppressing the expression of oxidative stress-associated genes (iNOS, NF- κ B, and COX2) [48]. Conversely, during opisthorchiasis infection, curcumin upregulates antioxidant defense genes (superoxide dismutase types 2 and 3, and catalase). These combined effects result in substantial improvement of hepatic histopathology through suppression of inflammatory infiltration and periductal fibrosis [49]. The authors propose that curcumin mitigates DNA damage by simultaneously suppressing inflammatory responses and restoring systemic oxidative balance during opisthorchiasis [48]. Recent findings reveal that nanoencapsulated curcumin–PZQ co-administration enhances therapeutic efficacy in hamsters, significantly reducing periductal fibrosis while preserving bile canaliculi morphology and maintaining normal bile acid metabolism gene expression – effects not observed with curcumin monotherapy [50]. Another study investigated both *in vitro* and *in vivo* anti-opisthorchiasis activity of a supramolecular curcumin–disodium glycyrrhizinate complex, demonstrating that the developed formulation induces more pronounced parasite immobilization and tegument damage compared to curcumin alone. *In vivo* evaluation showed the “curcumin–disodium glycyrrhizinate” complex exhibits moderate anthelmintic activity (50–60% parasite burden reduction), while being less efficacious than PZQ, yet significantly attenuates hepatic inflammation and fibrosis progression through its superior antioxidant and anti-inflammatory properties [19].

One of the central mechanisms in opisthorchiasis-

associated complications involves disruption of hepatic redox homeostasis, where the glutathione system – the primary antioxidant defense mechanism of hepatocytes – plays a pivotal role. Studies of chronic *O. felineus* infection demonstrate significant depletion of reduced glutathione (GSH) alongside increased oxidized forms (GSSG), promoting excessive reactive oxygen species accumulation, activation of pro-inflammatory signaling cascades, and stimulation of hepatic stellate cells, collectively driving fibrogenesis progression [51]. These findings validate pharmacological modulation of the glutathione system as a promising strategy for preventing opisthorchiasis-induced fibrosis, encompassing direct SH-group donors (N-acetylcysteine), glutathione synthesis stimulators, or complex antioxidants capable of restoring redox balance and interrupting the pathogenetic cascade of long-term invasion complications [51].

Another noteworthy research subject – the aqueous extract of blue trumpet vine (*Thunbergia laurifolia*) leaves – when administered to hamsters with experimental *O. viverrini* infection, suppressed inflammatory cell aggregation in peribiliary tissues while showing no hepatotoxicity. However, the extract itself demonstrated no significant direct anti-opisthorchiasis activity. Remarkably, co-administration of *T. laurifolia* extract with PZQ not only reduced inflammatory cell aggregation but also suppressed opisthorchiasis-associated cholangiocarcinoma development [52]. This effect may be attributed to decreased serum ALT levels, indicating reduced hepatocyte damage. The most significant results emerged when researchers administered the *T. laurifolia* extract not concurrently with PZQ, but rather following completion of standard anthelmintic therapy [53]. This sequential treatment protocol’s efficacy likely stems from suppression of either inflammatory reactions or host immune responses to parasite death. Indeed, the extract’s pronounced anti-inflammatory activity appears to modulate chronic infection-related immune reactions, improving hepatic histopathology and restoring organ function [53]. *In vitro* studies of *T. laurifolia* extract’s specific anti-opisthorchiasis activity against both juvenile and adult *O. viverrini* forms revealed decreased motility and survival rates at both stages. Scanning electron microscopy showed minimal tegumental alterations

compared to positive controls, despite significantly elevated reactive oxygen species levels [54].

Finally, a study investigating the antifibrotic properties of xanthohumol demonstrated that this polyphenolic compound – whether administered alone or in combination with PZQ – significantly reduced DNA damage, intracellular iron content, TfR-1 protein expression, and most importantly, decreased fibrotic areas [55]. The authors' findings suggest potential applications of xanthohumol combined with PZQ for preventing opisthorchiasis-associated cholangiocarcinoma development [55].

Considerable interest also surrounds the work by P. Pechdee et al., which conducted a comprehensive analysis of *A. sativum* (garlic) extract effects on isolated *O. viverrini* adult flukes [56]. The study revealed substantial increases in reactive oxygen species levels and structural damage to parasite bodies in *A. sativum*-treated groups. These findings correlated with overall motility reduction and increased mortality rates among mature flukes [56].

The combination of PZQ anthelmintic therapy with plant-derived bioactive compounds exhibiting anti-inflammatory, antioxidant, and hepatoprotective properties may substantially enhance anti-opisthorchiasis treatment efficacy. This combined approach not only potentiates antiparasitic effects but also mitigates pathological consequences of infection, including bile duct fibrosis, chronic inflammation, and oxidative stress.

Bioactive plant compounds (e.g., curcumin, silymarin, flavonoids, and polyphenols) demonstrate the ability to modulate immune responses, suppress proinflammatory cytokines (TNF α , IL-6), and reduce reactive oxygen species levels, thereby attenuating hepatobiliary system damage progression. Furthermore, their capacity to inhibit cell proliferation and angiogenesis may contribute to reducing cholangiocarcinoma risk – one of the most severe complications of chronic opisthorchiasis.

Indeed, the available scientific literature indicates that the redox status of both parasite and host, along with liver fluke-induced inflammatory responses, may represent primary biological targets for trematode infection treatment strategies.

CONCLUSION

Opisthorchiasis caused by the liver fluke *O. felinus* remains a significant public health

challenge, particularly in highly endemic regions, such as Western Siberia. Chronic parasite persistence in the hepatobiliary system associates with severe pathologies, including chronic cholangitis and progressive periductal fibrosis. PZQ, while remaining the therapeutic cornerstone for decades, exhibits fundamental limitations: complete lack of efficacy against larval developmental stages, potential hepatotoxicity during repeated treatment courses, growing threats of drug resistance development in endemic foci, and a scientifically debated yet potentially significant association between mass helminth die-off following PZQ administration and intensification of oxidative/nitrosative stress – established promoters of carcinogenesis.

As this lecture demonstrates, overcoming these limitations requires moving beyond PZQ monotherapy toward developing integrated, multi-target therapeutic strategies. The search for alternative synthetic compounds, such as tribendimidine, hybrid complexes (e.g., albendazole–arabinogalactan), or inhibitors of specific parasitic enzymes (*O. felinus* cytochrome P450) has revealed promising avenues. However, translating these agents into clinical practice remains challenging due to difficulties in converting encouraging *in vitro* results to *in vivo* efficacy, primarily stemming from complex pharmacokinetics and metabolic transformation issues. Within this context, plant-derived bioactive compounds gain particular importance. Their unique value derives not only from demonstrated direct anthelmintic activity (as seen with cynaropicrin), but critically from inherent polypharmacology enabling simultaneous targeting of key opisthorchiasis pathogenesis pathways: effective suppression of oxidative/nitrosative stress; modulation and mitigation of chronic inflammation through downregulation of proinflammatory cytokines (TNF α , IL-6) and mediators (iNOS, COX-2); reduced tissue infiltration thereby slowing fibrosis progression; and pronounced hepatoprotective effects improving hepatic histopathology and normalizing functional parameters.

The most promising and scientifically justified approach currently recognized involves combination therapy integrating PZQ's antiparasitic activity with the multifaceted effects of plant-derived antioxidants and anti-inflammatory agents. This synergistic strategy simultaneously

addresses multiple challenges: it potentiates PZQ's primary anthelmintic effect; neutralizes adverse consequences of massive parasite die-off, such as acute oxidative stress and extensive antigen release triggering systemic inflammation; and importantly, enhances overall treatment safety by enabling PZQ dose reduction and consequent toxicity mitigation.

Future research directions are clearly defined by current challenges and opportunities. Key priorities include: advanced development and optimization of combination regimens incorporating PZQ with specific phytocomplexes; precise determination of optimal dosages; evaluation of administration sequences (concurrent versus staggered); and assessment of long-term outcomes. Significant efforts focus on nanoencapsulation technologies to overcome bioavailability limitations and compound instability. Concurrently, screening of natural compounds continues to identify novel agents demonstrating direct anthelmintic activity against *O. felinus*, particularly those effective against PZQ-resistant juvenile forms.

Thus, effective opisthorchiasis control requires an integrative therapeutic paradigm. This approach harmoniously combines proven efficacy of classical anthelmintics with the multidimensional therapeutic impact of bioactive plant complexes. Addressing current treatment challenges necessitates developing comprehensive protocols capable of both reliably eradicating parasites at all developmental stages and protecting patients from the devastating long-term consequences of chronic infection.

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