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Comprehensive Review of PubMed Studies on myo-Inositol trispyrophosphate (ITPP)

Introduction

Myo-inositol trispyrophosphate (ITPP) is a synthetic myo-inositol phosphate in which three positions on the inositol ring are esterified with pyrophosphate groups. This structure gives ITPP a high negative charge and the ability to enter red blood cells (RBCs) through the band-3 anion exchanger. Inside RBCs it binds to hemoglobin and lowers the oxygen-binding affinity, increasing hemoglobin's P50. This enhanced oxygen release has been explored to treat cardiovascular hypoxia and tumours; ITPP has also drawn interest in sports due to its potential to enhance performance, leading to extensive efforts to detect it in doping control.

This review summarizes every PubMed-indexed study that is about or references ITPP (through May 2025). The studies are grouped into mechanistic/preclinical research, cardiovascular and pulmonary applications, cancer therapy and tumour oxygenation, clinical trials, and doping detection/veterinary research.

Mechanistic and Preclinical Studies

Allosteric effect of ITPP and RBC permeability (Chembiochem 2010)

- **Study:** *myo-Inositol trispyrophosphate: a novel allosteric effector of hemoglobin with high permeation selectivity across the red blood cell plasma membrane* (Chembiochem 2010).
- **Design and findings:** The authors synthesized ITPP and showed that it readily entered RBCs through the band-3 protein. Once inside, it bound hemoglobin and shifted the oxygen-dissociation curve to the right, reducing oxygen affinity. RBC ghosts bound ITPP with a dissociation constant of about 0.1 mM and ITPP modulated hemoglobin's P50 without affecting other cellular components [1].
- **Implications:** ITPP acts as a membrane-permeant allosteric effector of hemoglobin, providing a pharmacologic tool to increase oxygen unloading from RBCs.

Conservation of the Bohr effect (Blood Cells Mol Dis 2021)

- **Study:** *Modulation of red blood cell oxygen affinity with a novel allosteric modifier of hemoglobin is additive to the Bohr effect* (Blood Cells Mol Dis 2021).
- **Design:** Human RBCs were incubated with various ITPP concentrations (0–240 mM) at 37 °C for 1 h. P50 was measured under different pH conditions (6.8, 7.4, 7.6) using a Clark oxygen electrode. Linear-mixed models assessed the effects of ITPP and pH on P50.
- **Results:** Increasing ITPP concentration and decreasing pH both increased P50, indicating lower oxygen affinity [2]. The effect of ITPP was additive to the Bohr effect (acidosis-induced oxygen off-loading) and was absent at alkaline pH [3].

- **Implications:** ITPP enhances hemoglobin's ability to release oxygen while preserving physiologic pH-dependent regulation, supporting its safety for modulating oxygen delivery.

Stable vessel normalization via PTEN activation (J Mol Med 2013)

- **Study:** *Stable tumor vessel normalization with pO2 increase and endothelial PTEN activation by inositol trispyrophosphate brings novel tumor treatment* (J Mol Med Berl 2013).
- **Design:** Using melanoma and breast cancer mouse models, the study investigated whether ITPP could normalize tumour vasculature. ITPP was administered, and tumour oxygen tension and vascular morphology were assessed.

- **Results:** ITPP increased tumour oxygen tension and blood flow; it suppressed hypoxia-inducible factors, downregulated pro-angiogenic/glycolytic genes, and selectively activated endothelial PTEN, reducing PI3K/AKT signaling [4]. The compound promoted endothelial cell maturation, pericyte recruitment and decreased progenitor-cell recruitment, leading to stable vessel normalization and reduced vascular leakiness. These changes decreased tumour growth, drug resistance and metastasis [5]. The authors concluded that counteracting tumour hypoxia by stable vessel normalization with ITPP could complement anti-angiogenic therapies [6].

- **Implications:** The study provided mechanistic evidence that ITPP not only increases oxygen release but also reprograms endothelial cells via PTEN activation, leading to durable normalisation of tumour vasculature. This mechanistic insight underlies several subsequent cancer-oriented studies.

Cardiovascular and Pulmonary Applications

Enhanced exercise capacity in heart failure (PNAS 2009)

- **Study:** *Enhanced exercise capacity in mice with severe heart failure treated with an allosteric effector of hemoglobin, myo-inositol trispyrophosphate* (PNAS 2009).
- **Design:** Mice with severe heart failure and healthy controls received ITPP. Exercise capacity, hemoglobin P50, tissue oxygen levels and hemodynamics were measured.
- **Results:** ITPP administration increased hemoglobin P50 and maximal exercise capacity in both normal and heart-failure mice without changing blood pressure or cardiac contractility [7]. It decreased myocardial HIF-1α expression and improved tissue oxygenation [7].
- **Implications:** ITPP improved exercise tolerance by enhancing oxygen delivery, suggesting therapeutic potential for heart failure and other conditions with limited oxygen availability.

Treatment of hypoxia-dependent cardiovascular diseases (J Cell Mol Med 2020)

- **Study:** *Treatment of hypoxia-dependent cardiovascular diseases by myo-inositol trispyrophosphate – enhancement of oxygen delivery by red blood cells* (J Cell Mol Med 2020).
- **Design:** Rats with myocardial infarction received ITPP. Cardiac function and remodeling were evaluated. Cultured cardiomyocytes were used to investigate molecular mechanisms.
- **Results:** ITPP treatment improved post-infarction left-ventricular remodeling and protected against heart failure. In cultured cardiomyocytes, hypoxia up-regulated HIF-1α; perfusion with ITPP-loaded RBCs prevented this overexpression, linking improved oxygen delivery to decreased hypoxic signaling [8].

- **Implications:** The study suggested that ITPP therapy may protect cardiac tissue by delivering more oxygen and preventing HIF-1-mediated remodeling, representing a novel strategy for ischemic heart disease.

Prevention of right-ventricular failure in pulmonary hypertension (Br J Pharmacol 2024)

- **Study:** *myo-Inositol trispyrophosphate prevents right-ventricular failure and improves survival in monocrotaline-induced pulmonary hypertension in the rat* (Br J Pharmacol 2024).
- **Design:** Rats received monocrotaline to induce pulmonary hypertension, followed by ITPP treatment. Pulmonary hemodynamics, right-ventricular function and survival were assessed.
- **Results:** ITPP improved survival and prevented right-ventricular failure. It relieved right-ventricular hypoxia without affecting pulmonary vascular resistance, suggesting that improved oxygen unloading from hemoglobin was the primary mechanism [9].
- **Implications:** These findings support ITPP as an adjunct therapy for pulmonary hypertension focused on protecting the right ventricle rather than lowering pulmonary pressures.

Review of ITPP for cardiovascular disorders (Molecules 2022)

- **Study:** *myo-inositol trispyrophosphate (ITPP), from cancer to cardiovascular disease* (Molecules 2022).
- **Content:** This review summarized preclinical and early clinical evidence for ITPP. It noted that ITPP shifts the hemoglobin oxygen-dissociation curve to the right, increases oxygen release and tissue oxygenation, and has anti-angiogenic and anti-inflammatory effects. The review discussed potential uses in heart failure, pulmonary hypertension and cancer and reported that phase-II studies in patients were ongoing [10].

Cancer Therapy and Tumour Oxygenation

Increasing oxygen load reduces colon cancer growth (Oncogene 2013)

- **Study:** *Increasing the oxygen load by treatment with myo-inositol trispyrophosphate reduces growth of colon cancer and modulates the intestine homeobox gene Cdx2* (Oncogene 2013).
- **Design:** Mouse models of colon cancer (xenografts and genetically engineered Apc^+/Min mice) received ITPP. Tumour growth, survival and gene expression were evaluated.
- **Results:** ITPP increased tumour oxygenation and significantly reduced tumour growth and multiplicity while increasing survival [11]. It up-regulated the homeobox gene Cdx2 and reversed hypoxia-induced down-regulation of Cdx2 via PI3K/ERK pathway inhibition, indicating a mechanism linking hypoxia reversal to differentiation [11].
- **Implications:** The study linked improved tumour oxygenation to control of gene expression and differentiation, supporting ITPP as an adjuvant for colon cancer therapy.

Pancreatic cancer control and chemotherapy synergy (Int J Cancer 2014)

- **Study:** *myo-inositol trispyrophosphate-mediated hypoxia reversion controls pancreatic cancer in rodents and enhances gemcitabine efficacy* (Int J Cancer 2014).
- **Design:** Rodent models of pancreatic ductal adenocarcinoma received weekly ITPP alone or combined with gemcitabine chemotherapy. Tumour growth, metastasis, hypoxia markers and immune cell infiltration were measured.

- **Results:** ITPP restored tumour normoxia, down-regulated HIF-1α, VEGF and lysyl-oxidase, normalized vasculature and improved immune cell infiltration [12]. It inhibited metastasis and markedly enhanced the efficacy of gemcitabine [12].
- **Implications:** Reversing hypoxia with ITPP can sensitize pancreatic tumors to chemotherapy by normalizing the microenvironment and immune infiltration.

Inhibition of metastatic colon cancer (Ann Surg 2017)

- **Study:** *The allosteric hemoglobin effector ITPP inhibits metastatic colon cancer in mice* (Annals of Surgery 2017).
- **Design:** In murine models of colon cancer, ITPP was administered alone or with FOLFOX chemotherapy. Outcomes included tumour burden, circulating tumour cells and survival.
- **Results:** ITPP reduced tumour burden, decreased circulating tumour cells, improved survival and synergized with FOLFOX chemotherapy [13]. The authors advocated for clinical trials to test ITPP as an adjuvant therapy. [13]
- **Implications:** ITPP showed potent anti-metastatic activity and improved standard chemotherapy outcomes.

Tumour oxygenation and radiotherapy response (J Cell Mol Med 2019)

- **Study:** *Impact of myo-inositol trispyrophosphate on tumour oxygenation and response to irradiation in rodent tumour models* (J Cell Mol Med 2019).
- **Design:** Six tumour models were treated with ITPP. Tumour oxygenation was monitored by electron paramagnetic resonance oximetry and oxygen consumption rate (OCR); perfusion was assessed with Hoechst staining. Radiotherapy (RT) was combined with ITPP in rhabdomyosarcoma and 9L-glioma models.
- **Results:** ITPP enhanced tumour oxygenation in all six models. Two doses of 2 g/kg induced reoxygenation for at least four days. ITPP reduced OCR but did not change tumour perfusion [14]. Combining ITPP with RT showed benefit in a subset of 9L-gliomas but not in rhabdomyosarcoma [15].
- **Implications:** Improved oxygenation by ITPP may sensitize some tumours to RT, but the benefits appear model-dependent.

Radiotherapy scheduling (Int J Radiat Oncol Biol Phys 2021)

- **Study:** *Tumour oxygenation by myo-inositol trispyrophosphate enhances radiation response* (Int J Radiat Oncol Biol Phys 2021).
- **Design:** Murine tumour models received ITPP alone or combined with ionizing radiation. Tumour growth, oxygenation, DNA damage and immune cell infiltration were assessed.
- **Results:** ITPP alone did not affect tumour growth but increased tumour oxygenation. When administered before radiotherapy, ITPP enhanced radiosensitivity, increased DNA damage, improved immune infiltration and improved tumour control [16]. Scheduling experiments demonstrated that ITPP needed to be given before radiation to produce radiosensitization [16].
- **Implications:** Timing is critical for combining ITPP with radiotherapy; pre-treatment can exploit the oxygen therapeutic window to improve outcomes.

Failure to enhance radiotherapy in glioblastoma (Anticancer Research 2017)

- **Study:** *Failure of inositol trispyrophosphate to enhance highly effective radiotherapy of GL261 glioblastoma in mice* (Anticancer Research 2017).
- **Design:** Glioblastoma GL261 tumours were treated with radiotherapy alone or combined with ITPP. Survival and tumour growth were measured.
- **Results:** Radiotherapy alone significantly prolonged survival. ITPP alone had no effect, and the combination reduced the benefit of radiotherapy [17].
- **Implications:** ITPP may not be effective in all tumour types; in GL261 glioblastoma it did not improve and possibly impaired radiotherapy response.

Local pO_2 timing study (PLOS One 2023)

- **Study:** *Oxygen therapeutic window induced by myo-inositol trispyrophosphate – local pO_2 study in murine tumors* (PLOS One 2023).
- **Design:** Using B16 melanoma and 4T1 breast carcinoma models, researchers implanted OxyChip sensors and used electron-paramagnetic-resonance oximetry to measure intratumor oxygen partial pressure over several days after systemic ITPP administration.
- **Results:** ITPP increased tumour pO_2 by 10–20 mm Hg relative to control [18]. The oxygenation effect was transient or sustained depending on dose schedule and tumour type, and hypoxic tumours before treatment responded better [19]. The authors suggested that exploiting this oxygen therapeutic window could benefit therapies requiring oxygen, such as radio-, photo- or immunotherapy [20].
- **Implications:** The study quantified the duration of tumour reoxygenation after ITPP, guiding scheduling for combination therapies.

Immune checkpoint blockade synergy (Sci Rep 2025)

- **Study:** *Potentiation of immune checkpoint blockade with an ITPP radiosensitizer studied with oxygen saturation measurements from photoacoustic imaging* (Scientific Reports 2025).
- **Design:** CT26 colon and 4T1 breast tumour models received a radiosensitizer form of ITPP and immune checkpoint blockade (ICB). Photoacoustic imaging measured tumour oxygen saturation ($\%sO_2$), and immune cell populations were analyzed.
- **Results:** ITPP caused oxygen unloading from hemoglobin, increasing tumour oxygenation. Changes in oxygen saturation correlated with increased $CD8^+$ and $CD4^+$ effector T-cell frequencies and decreased monocyte frequencies [21]. Combining ITPP with ICB improved tumour control and survival [21].
- **Implications:** Improved oxygenation enhances antitumor immunity and suggests that ITPP can potentiate immunotherapy.

Clinical Trials and Human Studies

Phase Ib dose-escalation study (Nat Commun 2021)

- **Study:** *Phase Ib dose-escalation study of the hypoxia-modifier myo-inositol trispyrophosphate in patients with hepatopancreatobiliary tumors* (Nature Communications 2021).
- **Design:** Twenty-eight patients with hepatopancreatobiliary tumours received escalating doses of ITPP (OXY111A). Safety, tolerability, pharmacokinetics and preliminary efficacy were assessed.

- **Results:** The maximum tolerated dose was 12 390 mg m^{-2}; ITPP was generally well tolerated with minor hypercalcemia [22]. About half of patients experienced stable disease, and subsequent chemotherapy led to partial responses or stable disease in many cases [22].
- **Implications:** The trial demonstrated safety and hints of disease stabilization, justifying further studies.

First-in-human trial protocol (BMC Cancer 2016)

- **Study:** *Development of OXY111A, a novel hypoxia-modifier as a potential antitumor agent – protocol of a first Ib/IIa clinical trial* (BMC Cancer 2016).
- **Content:** The paper outlined the rationale and design of a dose-escalation study for OXY111A in patients with hepato-pancreato-biliary tumours. It reviewed preclinical evidence showing that ITPP normalized tumour vasculature, increased oxygenation and inhibited tumour growth, and described endpoints including safety, pharmacokinetics and initial efficacy [23].
- **Implications:** The protocol laid the groundwork for the 2021 trial and highlighted the transition from preclinical to clinical investigation.

Doping Detection and Veterinary Research

Detection in equine urine and plasma (Drug Test Anal 2012)

- **Study:** *Detection of myo-inositol trispyrophosphate in equine urine and plasma by hydrophilic interaction chromatography-tandem mass spectrometry* (Drug Testing & Analysis 2012).
- **Design:** A method based on solid-phase extraction and hydrophilic interaction chromatography tandem mass spectrometry (HILIC–MS/MS) was developed to detect ITPP in equine samples.
- **Results:** ITPP was isolated and detected at low parts-per-billion levels in fortified equine plasma and urine with good precision and minimal matrix effects [24]. This was the first validated method for detecting ITPP in any biological fluid [25].
- **Implications:** The method enabled detection of ITPP misuse in horseracing, a significant step for doping control.

Detection after administration in horses (Drug Test Anal 2014)

- **Study:** *Detection of myo-inositol tris pyrophosphate (ITPP) in equine following an administration of ITPP* (Drug Testing & Analysis 2014).
- **Design:** ITPP was administered intravenously to a mare. LC–MS/MS measured ITPP in plasma and urine over time.
- **Results:** ITPP was detectable in plasma up to 6 h and in urine up to 24 h post-administration [26], with peak concentrations at 5 min (plasma) and 1.5 h (urine) [26].
- **Implications:** The study provided detection windows for ITPP doping in horses and demonstrated the sensitivity of LC–MS/MS methods.

Screening and confirmation in human urine (Drug Test Anal 2014)

- **Study:** *Screening and confirmation of myo-inositol trispyrophosphate in human urine by hydrophilic interaction liquid chromatography high resolution / high accuracy mass spectrometry for doping control purposes* (Drug Testing & Analysis 2014).

- **Design:** Researchers developed a dilute-and-inject HILIC Orbitrap mass-spectrometry method for detecting ITPP in human urine.
- **Results:** The method achieved sub-nanogram per millilitre detection limits and exhibited high specificity and precision [27]. It demonstrated that ITPP is stable in urine under mandated storage conditions for doping control [28].
- **Implications:** This validated method allowed doping control laboratories to monitor for ITPP misuse in athletes.

Simultaneous detection of ITPP and bisphosphonates (Drug Test Anal 2025)

- **Study:** *Doping control analysis of myo-inositol trispyrophosphate and 10 bisphosphonates in equine plasma by ion chromatography–mass spectrometry* (Drug Testing & Analysis 2025).
- **Design:** An ion-chromatography–high-resolution mass spectrometry method was developed to simultaneously quantify ITPP and ten bisphosphonates in equine plasma.
- **Results:** The method achieved sub-ng/mL detection limits and was applied to an administration study of clodronic acid to validate performance [29]. It provided a single test to monitor multiple prohibited substances.
- **Implications:** Simultaneous detection enhances efficiency in doping control and addresses the concurrent use of ITPP and bisphosphonates in racehorses.

Extraction method optimization (Drug Test Anal 2025)

- **Study:** *Evaluating the effects of solid-phase cartridge chemistry on extraction of bisphosphonates and ITPP from equine plasma* (Drug Testing & Analysis 2025).
- **Design:** Different solid-phase extraction cartridges (mixed-mode vs polymeric phase) were evaluated for their ability to recover bisphosphonates and ITPP from equine plasma prior to LC–MS/MS analysis.
- **Results:** Recovery varied with cartridge chemistry; the study compared signal-to-noise ratios and recoveries and recommended the most effective approach for routine screening [30].
- **Implications:** Optimizing sample preparation enhances the robustness of doping detection methods for ITPP and related substances.

Human detection windows and doping concerns

- **Study:** *Detection of myo-inositol trispyrophosphate in equine urine and plasma by hydrophilic interaction chromatography-tandem mass spectrometry* (Drug Test Anal 2012) and *Screening and confirmation of myo-inositol trispyrophosphate in human urine* (2014) demonstrated detection windows and methods, but to date there have been no published cases of ITPP misuse in human athletes. The doping literature notes that ITPP is banned due to its oxygen-carrying potential and doping control laboratories continue to refine detection.

Discussion and Conclusions

The research on myo-inositol trispyrophosphate spans mechanistic studies, animal models, early-phase clinical trials and doping detection. Mechanistic studies establish that ITPP enters RBCs via band-3 and allosterically lowers hemoglobin's oxygen affinity without disrupting the Bohr effect [1] [31]. Vessel-normalization studies reveal that ITPP not only increases oxygen availability but also acts on

endothelial cells via PTEN activation, producing stable normalization of tumour vasculature, reduced metastasis and enhanced delivery of chemotherapy [32].

Across cardiovascular and pulmonary models, ITPP improves exercise capacity and prevents adverse cardiac and right-ventricular remodeling [7] [9]. These benefits translate into improved survival in heart failure and pulmonary hypertension models. The 2020 study showing HIF-1α suppression in cardiomyocytes suggests a common mechanism of hypoxia reversal [8]. A 2022 review summarizes these findings and highlights ongoing clinical trials [10].

In cancer models, ITPP consistently increases tumour oxygenation, reduces hypoxia signalling and normalises vasculature. These changes translate into slower tumour growth and enhanced responses to chemotherapy in colon and pancreatic models [11] [12]. Radiotherapy studies show that ITPP alone is not cytotoxic but can act as a radiosensitiser when given before ionising radiation, leading to increased DNA damage and immune infiltration [16]. The benefits are not universal; a 2019 investigation across six rodent tumour models found improved oxygenation but only selective benefit from combining ITPP with radiotherapy [14], while GL261 glioblastoma models even showed reduced benefit [17]. Timing and dosing are therefore critical, as illustrated by electron-paramagnetic-resonance oximetry studies that defined an “oxygen therapeutic window” lasting several days after ITPP administration [33]. Beyond radiotherapy, photoacoustic imaging studies demonstrate that ITPP-induced oxygen unloading enhances immune-checkpoint blockade [21], highlighting the potential for rational combination therapies.

Early clinical data demonstrate tolerable safety profiles and hints of tumour stabilization [22]. Further phase-II/III trials are needed to assess efficacy in specific cancers and to optimize dosing schedules.

Due to its oxygen-releasing properties, ITPP has attracted attention as a potential doping agent. A series of studies have developed sensitive methods to detect ITPP in equine and human samples [24] [27] and, more recently, simultaneous detection of ITPP with bisphosphonates [29]. These methods are important to prevent misuse in sports.

Overall, myo-inositol trispyrophosphate emerges as a versatile hypoxia modifier that enhances oxygen delivery by modulating hemoglobin. Preclinical studies show promising therapeutic effects in cardiovascular disease and cancer, and early clinical data support further investigation. At the same time, the compound’s performance-enhancing potential necessitates sensitive doping detection methods to ensure fair competition in sports.

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