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Review Article

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The Pharmacological and Clinical Effects of Pentoxifylline on Pet Animals

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Abstract

Plenty of restorative plants including phenols, essential oils, flavonoids, glycosides, and amides, have been assessed for therapeutic effects against several diseases especially liver diseases. Pentoxifylline (PTX), a methyl-xanthine spin-off with a variety of anti-inflammatory and protective actions in animals. PTX has been found effective for many disease conditions. PTX is an immune-modulatory agent used in the treatment of immune-mediated diseases blood vessels inflammation such as cutaneous lupus in canine and navicular disease in horses. It also has hepato-protective effect, so it could be used to treat liver fibrosis and embolism in pet animals. Moreover, it could be used in the treatment of vessels ulcers through improving healing and microcirculation. This review highlighted numerous vital characteristics of PTX and its therapeutic role in various diseases in pet animals.

KEYWORDS
Pentoxifylline, PTX, Silymarin, Hepatoprotective evaluation, Veterinary impact.

INTRODUCTION

Pentoxifylline, (PTX), known as oxpentifylline, is a derivative of the methyl-xanthine group with a variety of anti-inflammatory properties. Yet, use and efficacy of PTX for a variety of conditions has been verified in various studies over an elongated period, (FDA) has permitted its usage merely for intermittent claudication (IC). In medicine, it primarily used to alleviate pain, and lessen weakness in the extremities that happens because of IC, PXF is safer than other ordinary hepatic protective drugs as may be used for treatment of liver cirrhosis and embolism in pet animals (Hassan *et al*., 2014).

PTX has found application in various disease processes; although, the mechanism is not fully elucidated in such cases. PTX is used for treatment of neuropathic, thrombo-embolic and septic disorders (Zeni, 1996). Furthermore, it can also be applied as a conservative treatment for hepatic diseases, endometriosis, and sickle cell disease via inhibition of tumor necrosis factor (TNF) (Mohammadzadeh *et al*., 2007).

In fact, in dogs with hered-itary platelet function defects that exhibit weak platelet aggregation during aggregometry, the addition of the luciferin–luciferase reagent causes adose-dependent potentiation of platelet aggregation, Canine platelet function has previously been shown to be inhibited by a range of phosphodiesterase inhibitors, so Pentoxifylline is known to be a non-selective inhibitor of PDEs (Thomason *et al*., 2021).

In human medicine, pentoxifylline has been used as an adjuvant medication for the treatment of pemphigus vulgaris since it has been shown to inhibit TNF-alpha, playing a partial role in the pathogenesis of the disease (Tham *et al*., 2020).

Chemical structure

PTX is 3,7-dimethyl-1- (5-oxohexyl)-3,7-dihydro- 1H-purine-2,6-dione and its chemical formula is $C_{13}H_{18}N_4O_3$. The structure is displayed in Fig. 1.

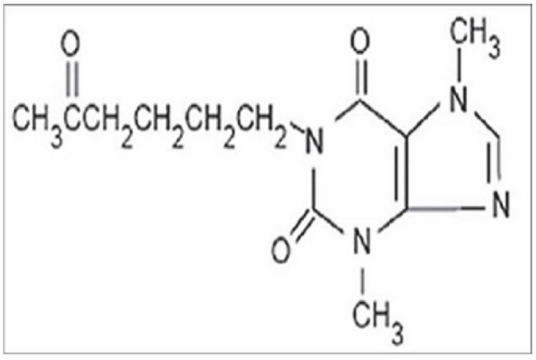

Fig. 1. The Chemical composition of PTX.

Pharmacokinetics and Metabolism

Once PTX administered orally the aqueous portion of PTX is absorbed and goes through metabolism and consequently several metabolites begin to rise in plasma directly after adminis-

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tration; plasma level reaches peak within 2 hours. The foremost metabolites are metabolite-I [1-(5-hydroxyhexyl)-3, 7-dimethylxanthine] and metabolite V [1-(3-carboxypropyl)-3, 7-dimethylxanthine]. The levels of these metabolites are respectively 5- and 8-times superior to PTX. Excretion is almost completely via urine where metabolite V is the main excreted product, and its recovery is consistent and dose dependent. Additionally, less than 4% of the applied dosage is recovered in the fecal matter (Ward and Clissold, 1987). At the present time, the usual recommended pentoxifylline dosage is as follows: one 400mg controlled release tablet (Trental), two or three times daily. Studies on efficacy of pentoxifylline indicate that clinical improvement becomes apparent usually two to four weeks after initial oral use. It follows that the drug should be administered for at least four weeks and discontinued if there is no clinical improvement. This period appears to be necessary for recompensating of the patho-hemorheologic abnormality in ischemic tissue. The two to four weeks latent period for therapeutic effect of a hemorheological drug also occurs in experimental rats. Pentoxifylline reduces the extent of necrosis and hastens the repair of pedicle flaps surgically prepared in the rat, and this is apparent within one to two weeks. Also in the rat, the drug almost immediately elevates erythrocyte adenine nucleotide content, presumably associated with an increase in flexibility. (Aviado and Dettelbach, 1984).

Mechanism of Action

There are various hypotheses about the mechanism of action of PTX and its molecular and cellular belongings. This embraces effects on immune inflection, anti-tumor necrosis factor-α (TNF-α) belongings, hemorheological properties, anti-fibrinolytic effects, along with actions on endothelial cells and adhesion particles.

Different mechanisms of action may include

Immune modulation

PTX moves immune inflection by incomes of augmented leukocyte chemotaxis, diminished endothelial-leukocyte linkage, reduced degranulation of neutrophil and release of superoxide, decreased release of monocyte-resultant TNF, lowering leukocyte sensitivity to interleukin 1 (IL-1) and TNF (Samlaska and Winfield, 1994). PTX could be used in treatment of COVID-19 patients by reduction of the pro-inflammatory cytokines production (DiNicolantonio and Barroso-Aranda, 2020). PTX is considered as a non-selective phosphodiesterase inhibitor which leads to stimulation of protein kinases and down-regulating the expression of angiotensin 1 receptor (AT1R) which leads to blockage of pro-inflammatory cytokines and influence the renin-angiotensin system (RAS), respectively (Maldonado *et al*., 2020).

Anti-TNF-α properties

PTX inhibits the release of TNF-α, which part of it is a vital inflammatory intermediary with a widespread range of action, chiefly derived from mononuclear cells. PTX is likewise selective inhibitor of previously molded TNF. PTX may also impact additional pro- inflammatory cytokines such as IL-1 and IL-6 (Van Furth *et al*., 1994). Most recent study evaluated the effects of pentoxifylline (PTX) on acute lung injury (ALI) in dogs, and they found that the TNF-alpha and IL-8 levels in PTX-treated dogs were significantly lower than the dogs received lung protective ventilation treatment (Duan *et al*., 2007). Additionally, the reducing effect of PTX on TNF-alpha, it could be as a therapeutic nephroprotective drug of in case of gentamicin nephrotoxicity (Mousavinasab *et al*., 2021). Pentoxifylline is recognized as an inhibitor of TNF-α, an important mediator of inflammation (Alyssa, 2017).

Hemorheological properties

PTX touches nearly the entire features accountable for viscosity of blood and is amid the first identified hemorheological effective drug (Ely, 1988). The crucial hemorheological actions of PTX are produced by improving deformability of RBCs and decreasing the viscosity of blood. This action may be attributed to elevated erythrocyte adenosine triphosphate (ATP) and other nucleotides by PTX (Porsche and Stefanovich, 1978). PTX tips to reduction of thromboxane yet increase of prostacyclin production. Hypercoagulability conditions expand because of lessened aggregation and adhesion of the blood platelets; elevated plasminogen enhancer, plasmin and anti-thrombin III; decreased fibrinogen, alpha 2-antiplasmin, alpha-2 macroglobulin, and alpha-1 antitrypsin (Samlaska and Winfield, 1994). Besides, PTX increases leukocyte to become distorted, inferring the likelihood of a superior role of PMNL in whole blood viscosity (Ely, 1989). Consequently, it fires as well thought out as almost complete rheological medicine (Dettelbach and Aviado, 1985). Hemorheological effect of pentoxifylline is a reduction in fibrinogen level. The observed effect would reduce plasma viscosity and contribute to the overall reduction in whole blood Viscosity. The actual reduction of fibrinogen level is reversible and has not been reported to cause intractable bleeding in treated patients (Aviado and Dettelbach, 1984). Pentoxifylline would inhibit canine platelet function by reducing platelet aggregation, and that the addition of a luciferin luciferase reagent would obscure detection of pentoxifylline-induced platelet dysfunction as measured via aggregometry (Thomason *et al*., 2021).

Anti-fibrinolytic effects

PTX raises fibroblast collagenases plus cuts the production of collagen, fibronectin, and glycosaminoglycan (Berman and Duncan, 1989). These personal properties could be credited to the anti TNF-α assets or distinct mechanisms as proposed by several studies (Berman *et al*., 1992). PTX is found to inhibit the extra-cellular matrix deposition and helps in re-ordering of the collagen fibers in case of Hypertrophic scars (HS) (Yang *et al*., 2019). Another study concluded that systemic administration of PTX enhances the rate of re-epithelization and decreasing the necrotizing parts of the burns (Yucel *et al*., 2019). Pentoxifylline does not exert an in vitro inhibitory effect on canine platelet aggregation using collagen as an agonist (Thomason *et al*., 2021). Pentoxifylline is a methylxanthine derivative that is used in human and veterinary medicine for its hemorheological effects and anti-inflammatory properties. This methylxanthine derivative functions to decrease blood viscosity by reducing plasma fibrinogen levels and promoting fibrinolytic activity (Ali and Carman, 2012).

Clinical Applications in Various Aspects in Medicine

Peripheral vascular diseases (PVD)

PTX has been recycled worldwide for the handling of IC and in 1984; FDA approved its usage for IC in the USA. Countless revisions have publicized the beneficial effectiveness of PTX in a noteworthy percentage of patients with PVD (Chopra, 1988).

Nonetheless, practice in IC quiet leftovers the chief indication (Bayer *et al*., 1996). Intravenous PTX may be of assistance in serious ischemic lesions in general sclerosis, when used as 1200 mg/day for 21 days (Goodfield and Rowell, 1989). The improvement in blood flow in the ischemic limb induced by pentoxifylline is hemorheological in nature. (Muller, 1981). Improvement in capillary circulation is brought about by the primary action of the drug, i.e., increase erythrocyte flexibility. In turn, this increase in erythrocyte flexibility reduces whole blood viscosity which is directly related to vascular resistance; according to Poiseuille's equation reduced viscosity can decrease resistance to blood flow (Aviado and Dettelbach 1984). A single dose of pentoxifylline in dog did not detectably inhibit platelet aggregation using optical aggregometry (Rees *et al*., 2003). In human medicine, pentoxifylline is mainly used in the treatment of peripheral arterial disease (PAD) along with certain cerebrovascular diseases that lead to reduced blood flow to brain tissue. In veterinary medicine, pentoxifylline has been prescribed for similar conditions; however, the medication is thought to be effective in treating other disorders (Alyssa, 2017).

Vasculopathies

As PTX had manifold properties on numerous blood cells and through anti-inflammatory actions, it can be a valuable agent for treatment of vasculopathies as described by Marzano *et al*. (2003). PTX might be considered a useful therapeutic option for attenuating the aortic calcification associated with atherosclero-

Table 1. Summary on the role of the impact of Pentoxifylline (PTX) on the treatment of some pet animals' diseases.

Type of disease	Dose of Pentoxifylline (PTX)	Pharmacological and clinical effects of pentoxifylline
1- Canine atopic dermatitis (CAD) (Scott and Miller 2007). The treatment of CAD is multifaceted and consists of a combination of actions that include the use of allergen avoidance, anti- inflammatory drugs, allergen-specific immunotherapy, and antimicrobial drugs (Scott *et al*., 2001). PTX was found to be a useful nonsteroidal antipruritic agent for the control of pruritus in dogs with CAD. It was effective as a stand-alone drug, as a steroid-sparing drug, and in combination with allergen-specific immunotherapy. Side effects were rare and mild (Scott and Miller 2007).	Thirty-seven dogs with chronic canine atopic dermatitis (CAD) were treated with pentoxifylline (PTX), 25 mg/kg every 12 hours, given orally with food for at least 4 weeks (Scott and Miller, 2007). As PTX is rapidly absorbed when given orally, with a bioavailability of about (20 to 30%) (Rees *et al*., 2003) Absorption and bioavailability are not affected when the drug is given with food (Rees and Boothe, 2003).	PTX acted as Anti-inflammatory and immunomodulatory (Scott and Miller 2007) such as: 1- Decreased leukocyte adhesion to keratinocytes and endothelial cells (down regulation of adhesion molecules ICAM-1 & LFA-1). 2- Decreased neutrophil degranulation and superoxide release Decreased natural killer-cell activity. 3- Decreased interleukins (IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12) Decreased tumor necrosis factor-alpha (TNF-α). 4- Decreased interferon-gamma (IFN-α).
2-Use of pentoxifylline in the treatment of allergic contact reactions to plants of the Commelinceae family in dogs. Pentoxifylline represents an alternative strategy for the management of contact allergy. in dogs when avoidance is not possible, and corticosteroids are ineffective, or side-effects are unacceptable to the owner or the patient. (Marsella *et al*., 1997).	The effects of pentoxifylline (10 mg kg^{-1} orally [PO] twice daily) in three dogs with a confirmed contact allergy to plants of the Commelinceae family. The average duration of therapy was 4 weeks (Marsella *et al*., 1997)	Pentoxifylline has been used for the treatment of dermatomyositis with variable success (Hargis and Mundell, 1992). The proposed mechanism is an increase in tissue oxygenation through increased microvascular blood flow. After administration of the drug, plasma levels of the drug reach a maximum within 2-4 h. After absorption, pentoxifylline undergoes a first pass effect. The initial metabolite is formed by the erythrocytes at the membrane and the other six metabolites are formed in the liver by oxidation and demethylation. Extensive enterohepatic recycling occurs and more than 90% of the absorbed drug is excreted in the urine in the form of metabolites. (Marsella *et al*., 1997).
3- Double-blinded cross-over study on the efficacy of pentoxifylline for canine atopy. During PTX treatment, scores of pruritus and erythema decreased significantly (Marsella and Nicklin, 2000)	(10mg kg^{-1} twice daily for 4 weeks) (Marsella and Nicklin, 2000)	Pentoxifylline has numerous immunomodulatory and anti-inflammatory properties. The initial rationale for the use of PTX in canine atopy was to induce suppression of pro-inflammatory cytokines (e.g. TNF-α, IL-1 and IL-б) which play a role in the inflammatory cascade triggered by the allergic reaction (Marsella and Nicklin, 2000).
4- A retrospective study of canine and feline cutaneous vasculitis Cutaneous necrotizing vasculitis is a rare disorder of dogs and cats which is generally defined as a disease process characterized by inflammation and subsequent destruction of blood vessels resulting in ischaemic necrosis of recipient tissue (Nichols *et al*, 2001).	The dosage of pentoxifylline (10 –15 mg kg^{-1}) used interval (twice daily) (Nichols *et al*, 2001).	Pentoxifylline, has proven to be of significant benefit for the treatment of numerous dermatoses of human beings. In the treatment of cutaneous vasculitis, the most substantial effect of this drug may be its potent haemorrheologic properties which increase erythrocyte deformability, thus allowing the cells to pass through compromised blood vessels more readily. Pentoxifylline has also shown significant anti-inflammatory effects due to inhibition of pro-inflammatory cytokines [interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-α], direct inhibition of leukocyte adhesion to endothelial cells, inhibition of chemokines and inhibition of leukocyte adhesion to keratinocytes (Nichols *et al*., 2001).
5- Successful management of feline pemphigus foliaceus with pentoxifylline and topical hydrocortisone aceponate. The first case of feline pemphigus foliaceus (PF), an autoimmune disease caused by auto-antibodies against proteins of the desmosome junction in China (Hobi *et al*., 2022).	The effective alternative treatment approach consists of pentoxifylline (26.5 mg/kg q12h PO; Pentoxifylline 400mg®) and topical hydrocortisone aceponate in a patient with a history of a severe systemic infectious disease (Hobi *et al*., 2022).	Pentoxifylline has been used as an adjuvant medication for the treatment of this disease since it has been shown to inhibit TNF-alpha that is playing a partial role in the pathogenesis of the disease (Hobi *et al*., 2022).

sis. This was assessed by down-regulation of bone morphogenetic protein-2 (BMP-2), wingless-type MMTV integration site family 3A (Wnt3a) mRNA levels and osteopontin expression in the aortic tissue (Elseweidy *et al*., 2019). This agent is well thought out as suitable material for treating venous leg disease (Margolis, 2000) and venous ulcers, particularly the patient incapable to tolerate compression therapy (Chatterjee, 2012). Pentoxifylline is also capable of influencing hemostasis in canine (Rees and Boothe, 2003). Pentoxifylline causes a primary increase in cardiac output which is compensated by reflexogenic systemic vasodilation and reduction in total systemic vascular resistance, i.e., cardio-aortic baroreceptor inactivation might occur in response to augmented cardiac output. So, the intravenous injection of pentoxifylline causes a reflexogenic vasodilation. Pentoxifylline is regarded as a promising drug in the treatment of circulatory ischemic disorders, especially in intermittent claudication (Aviado and Dettelbach 1984).

Pigmented purpuric dermatoses (PPD)

Prosperous treatment with PTX grounds reduction in ICAM-I expression of endothelial cells in and around PPD lesions (Kano *et al*., 1997) ensuring in decreased excavation of inflammatory cells from blood capillaries into the adjacent tissues and likewise reduced TNF mediated extravasations (Ely, 1994). PTX actuality economical, easily available and lacking severe side-effects would be deliberated for usage in Schamberg's disease, a type of PPD; some promoter it as first line treatment (Panda *et al*., 2004). In dogs, it is mostly used to treat dermatologic syndromes such as vasculitis and familial dermatomyositis (Marsella *et al*., 2000).

Aphthosis and Behcet's disease

PTX has been established active in regular oral and genital Aphthosis (Thornhill *et al*., 2007). The advantageous properties might be because anti-TNF-α possessions of PTX as well as alteration of impaired erythrocyte deformability which has been exposed, to be decreased in active Behçet's disease patients in comparison with control individuals (Usküdar *et al*., 2005). Pentoxifylline might alleviate the inflammatory response necessary for development of the arterial plaques (Alyssa, 2017).

Leprosy

Several trials have acknowledged that PTX amends systemic indicators of type II leprosy response, and it could be substitute (though less effective) to thalidomide (Nery, 2000), and a decent choice for patients with human immunodeficiency virus (HIV) co-infection, where steroids are prohibited (Chatterjee and Jaiswal, 2002).

Acquired immunodeficiency syndrome HIV/AIDS

PTX is well thought-out as nontoxic, efficacious agent for HIV-infected patients. Additional controlled trials are needed to validate it (Berman *et al*., 1998). This might be due to its inhibitory action on TNF-α, which is overexpressed in many patients with AIDS (Lähdevirta, 1988). It likewise decreases HIV replication (Dezube *et al*., 1993). Pentoxifylline is capable of inhibiting neutrophil adhesion and activation while decreasing levels of tumor necrosis factor alpha (TNF-α), an early inflammatory mediator. (Alyssa, 2017). In order to avoid significant suppression of the Th1 immunity by conventional therapy and because of its efficacy in treatment of human pemphigus vulgaris, pentoxifylline was added (Kummari *et al*., 2020).

Graft-versus-host disease (GVHD)

It is well known that the inflammatory cytokines involving TNF-α as well as cytotoxic T. lymphocytes significantly mediate in the occurrence of GVHD. Use of PTX in arrangement with extra therapies might end in lower rates of relapses and enhanced overall the survival rates. Nevertheless, prophylactic role of PTX in GVHD is conflicting (Clift *et al*., 1993). In dogs, PTX alleviates injuries after lung allotransplantation via it prevents graft endothelial dysfunction and inhabits activation and migration of neutrophil into pulmonary tissue (Yamashita *et al*., 1996).

Radiation induced fibrosis, burns and oral fibrosis

Radiation made fibrosis is arbitrated by TGF-β (Rodemann and Bamberg, 1995), besides its dominant role in scleroderma (Sollberg and Krieg, 1995). PTX and vitamin E could be effectively used, as cost-effective, in treatment of the fibrosis that is a result of radiation, particularly for inoperable patients (Fischer *et al*., 2001). PTX was found to have a direct consequence on inhibition of fibroblasts during burn scare formation. Besides, it can be hypothetically effective for decreasing contractures of the formed burn scar (Rawlins *et al*., 2006). The efficacy of PTX in oral submucosal fibrosis (singly and as adjuvant therapy) has been demonstrated in various studies (Mehrotra *et al*., 2011).

Ulcerating necrobiosis lipoidica (NL) and Pretibial myxedema (PTM)

Ulcerating NL is a chronic granulomatous disorder that is of unknown cause and rarely affects skin (Erfurt-Berge *et al*., 2021). The efficacy of PTX for necrobiosis lipoidica has been documented in various studies, probably because it inhibits platelet aggregation and decreases blood viscosity (Basaria and Braga-Basaria, 2003). Previous report has also demonstrated successful treatment of NL with PTX at different clinical stages of the disease (Wee and Kelly, 2017). The autoimmune disorder PTM is identified by deposition of glycosaminoglycans in the skin dermis (Chen *et al*., 2021). Since PTX has anti-fibrinolytic effect, it could be useful in, either with topical or intra-lesional steroids, treatment of pretibial myxedema as well as helps in reducing the thickness of skin lesions (Engin *et al*., 2007).

CONCLUSION

PTX is a moderately safe and effective therapeutic drug as well as potential uses in several hemorheological and other related disorders. It could be used either singly or as an adjuvant therapy in pet animals. Although several studies have been conducted to prove the beneficial effects of PTX, there is paucity of data to determine its beneficial role in various hemorheological diseases. PTX might be beneficial for liver cirrhosis and embolism in pet animals' experimental trials that should be held to enroll it as a candidate for such cases.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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