International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 9 (4): 245-250, 2013
ISSN 1811-7775 / DOI: 10.3923/ijp.2013.245.250

A Review on the Role of Oxidative Stress and Inflammation in Necrotizing Enterocolitis and Benefits of the Phosphodiesterase Inhibitor Pentoxifylline

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Abstract: The condition of activated inflammation in the intestine is known as Necrotizing Enterocolitis (NEC) which is more frequent in premature infants. Various studies have being carried out to find effective protections or therapies based on recognized pathophysiology of the disease. In the present review, all possible mechanisms and existing evidences at experimental or clinical levels have been analyzed. The main target is the modulation of inflammation by use of immune modulators and anti-oxidants. Pentoxifylline (Ptx) exhibits immunomodulatory effects via decreasing the synthesis of tumor necrosis alpha (TNF-α), interlukin-6 (IL-6), interferon-gamma (INF-γ) and other pro-inflammatory cytokines. It exerts anti-oxidant properties via scavenging hydroxyl radicals and inhibiting the xanthine oxidase. Therefore Ptx is deemed an option in the management of NEC in premature infants if proper clinical trials confirm its safety in neonates.

Key words: Inflammatory bowel disease, oxidative stress, pentoxifylline, phosphodiesterase inhibitor, premature infants

INTRODUCTION

Necrotizing enterocolitis: A highly activated inflammatory response resulting in disruption of intestinal epithelium and bowel necrosis is known as Necrotizing Enterocolitis (NEC). NEC is considered as one of prevalent emergency conditions mostly occurring in premature neonates. It affects approximately 10% of premature infants<1500 g (Claud, 2012), accompanied with high mortality and/or morbidity rate. Some of known common symptoms are diarrhea, feeding intolerance, abdominal distention and bloody stools. Alongside the aggravation of inflammation, intestinal perforation, peritonitis and systemic hypotension occur and patients require intensive medical care. Regardless of various attempts, the exact cause of NEC still remains challenging. However, some of the pathophysiological mechanisms that have been suggested so far are illustrated in the Fig. 2-4. However three main mechanisms can be described.

The first symptom of NEC is a reduction of blood flow in the intestine, which results in intestinal ischemia. This hypoxia condition is usually made by oxygen-derived free radicals and hydroxyl radicals by the mediation of xanthine oxidase. These substances, besides

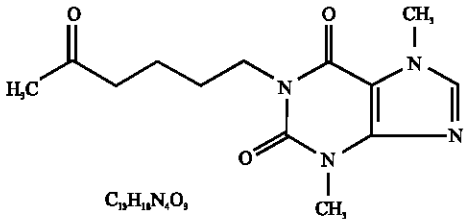

Fig. 1: Structure of pentoxifylline ($C_{13}H^{18}O_3$)

leukocyte-derived free radicals, altogether, lead to an oxidant-mediated lipid peroxidation injury which is responsible for necrosis of intestine. Additionally, free radicals may increase vascular permeability and release of prostaglandins and leukotrienes (Okur *et al*., 1995; Erdener *et al*., 2004; Shah and Sinn, 2012; Caplan *et al*., 1990; Harpavat *et al*., 2012; Parks and Granger, 1983; Ciuffetti *et al*., 1991; Rezaie *et al*., 2007) (Fig. 2).

Another involved factor is over-activity of the immune system and an imbalance between activated pro-inflammatory responses with anti-inflammatory protection. Consequently, the augmented cytokine release, the increased level of tumor necrosis factor alpha (TNF-α), as a key factor for inflammation cascades and an activation of toll like receptor-4 (TLR-4) have been demonstrated to contribute in the aggravation of

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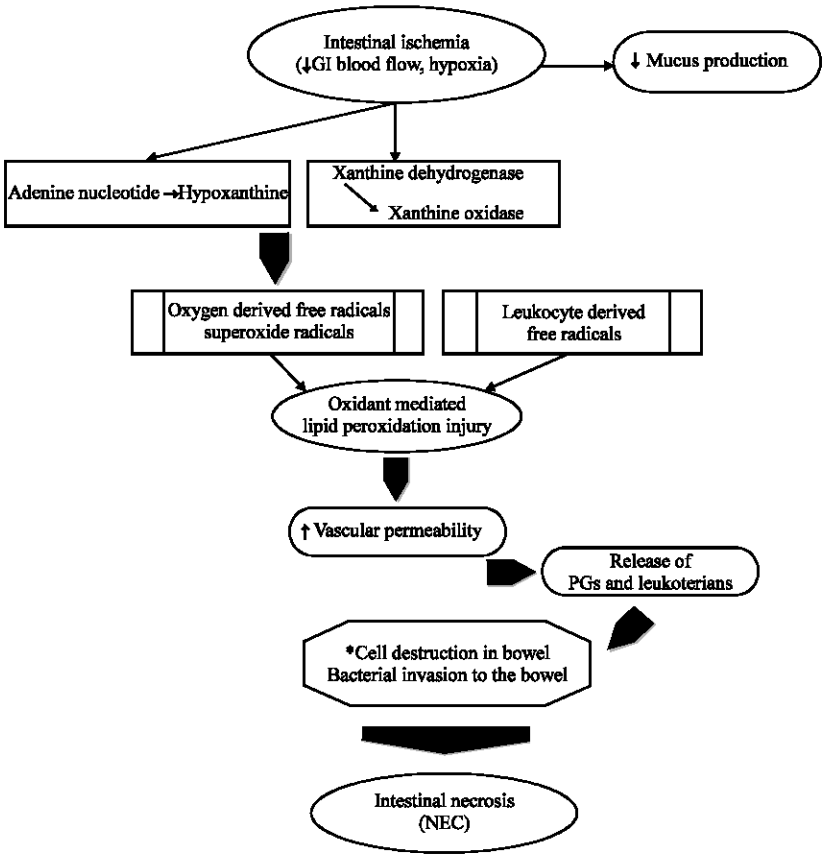

Fig. 2: Intestinal ischemia as a pathophysiological mechanism in NEC, GI: Gastrointestinal; PG: Prostaglandins

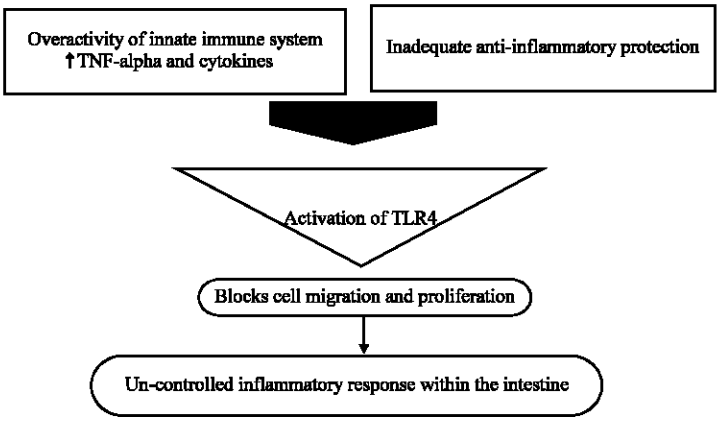

Fig. 3: Over-activity of immune system in NEC, NEC: Necrotizing enterocolitis; TLR: Toll like receptor; TNF: Tumor necrosis factor

the inflammatory response in the intestine (Travadi *et al*., 2006; Arciero *et al*., 2013; Uguralp *et al*., 2004; Guven *et al*., 2009a) (Fig. 3).

Furthermore, reduced production of mucus besides the alteration of mucosal defenses and intestinal microbiota may bring about infection and bacterial translocation which contributes to gut injury via disruption of intestinal integrity. Inducible nitric oxide (iNOS) is also thought to induce enterocytes apoptosis that impairs mucosal barrier

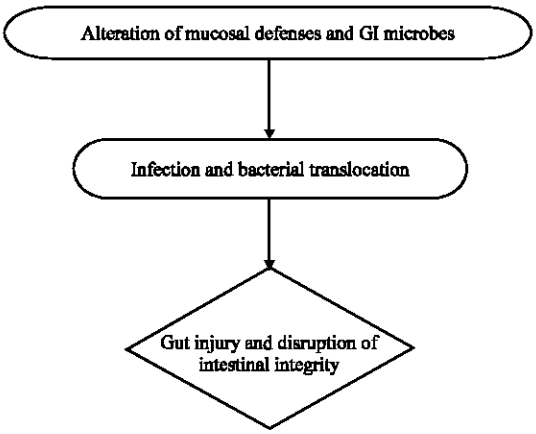

Fig. 4: The role of intestinal microbiota in development of NEC, GI: Gastrointestinal; NEC: Necrotizing enterocolitis

and bacterial translocation (Luedtke *et al*., 2012; Ergun *et al*., 2007) (Fig. 4).

Considering the relatively high mortality and morbidity of NCE, its prevention and treatment has become a field of interest in many clinical and experimental investigations (Patole, 2007). Although the exact pathophysiology of NEC is still unclear, due to the associated multifactorial causes and risk factors, various regimens have been successfully used. Modulation of inflammation by Platelet Activating Factor (PAF), interferon (INF) and glucocorticoids (Harpavat *et al*., 2012; Patole, 2007) are among the options. In addition, Ptx, vasoactive substances (Harpavat *et al*., 2012) and reducing the vascular permeability are among therapeutic strategies for the management of NEC (Parks and Granger, 1983). Targeting and modulation of the intestinal defenses, dietary and bacterial factors is effective in NEC treatment (Lin and Stoll, 2006). Several antibiotics have been used in addition to probiotics. Today, probiotics have been demonstrated to prevent development of NEC (Shah and Sinn, 2012; Patole, 2007).

To find more substances with beneficial effects, several investigations have been performed on experimental models. The details are summarized in the Table 1.

PENTOXIFYLLINE

Ptx (Fig. 1) is a tri-substituted purine (1-(5-oxohexyl)-3,7-dimethylxanthine) methyl xanthine derivative that besides its phosphodiesterase inhibitory effect, improves blood rheology and viscosity by inhibiting platelet aggregation and increasing blood cells flexibility. Phosphodiesterase inhibitors have been demonstrated to be effective in different inflammatory conditions and protect cells from oxidative-stress (Freitas and Filipe, 1995; Badri *et al*., 2011; Rahimi *et al*., 2010; Ghiasi *et al*., 2012).

In addition, Ptx exhibits immunomodulatory effects via decreasing the synthesis of TNF-α, interlukin-6 (IL-6), INF-γ and other pro-inflammatory cytokines throughout mucosal injury or sepsis. In the recent years, different phosphodiesterase inhibitors have been found beneficial in inflammatory bowel disease (Travadi *et al*., 2006; Patole, 2007; Harris *et al*., 2010; Lauterbach *et al*., 1999; Haque and Pammi, 2003; Salari and Abdollahi, 2012; Salari-Sharif and Abdollahi, 2010).

Ptx exerts its anti-oxidant properties by scavenging hydroxyl radicals and xanthine oxidase inhibition (Erdener *et al*., 2004; Salari and Abdollahi, 2012; Rezvanfar *et al*., 2012; Khoshakhlagh *et al*., 2007). It is believed to inhibit the generation of free radicals from leukocytes and the release of reactive oxygen metabolites during peripheral ischemia (Ciuffetti *et al*., 1991).

In this respect, Ptx has been used in several inflammatory infectious and vascular diseases (Harris *et al*., 2010; Rezvanfar *et al*., 2012). In addition, Ptx has been used in several clinical studies as a treatment option in shock and sepsis. Although, Haque and Pammi (2011) observed that Ptx may decrease the duration of disease in infants with sepsis but it does not affect the risk of development and incidence of NEC (Haque and Pammi, 2011). Some other reports demonstrate an increased incidence of NEC in placebo group of infants with sepsis which did not receive Ptx (Lauterbach *et al*., 1999; Lauterbach and Zembala, 1996).

Ptx has also been introduced as a therapeutic option to reduce the mortality and morbidity in premature infants with NEC (Harris *et al*., 2010). Given the immunomodulatory effects and demonstrated anti-oxidant and free radical scavenging effects of Ptx, it may comprise considerable potential to be in the package for management of NEC (Table 2).

METHODS

In this stduy we have reviewed the pathophysiology of NEC and evidences for the beneficial effect of anti-oxidant therapy and Ptx in this disease. In order to collect all evidences including experimental investigations and clinical trials, we used broad databases such as Google Scholar, PubMed, Scopus and Web of Science without date limitations.

RESULTS AND EVIDENCES

As summarized in Table 1, several studies have established animal models of ischemia and oxidative stress to induce NEC in the rat. These models mainly

Table 1: Experimental studies on the efficacy of several drugs on NEC

Study	Model	Investigated substance	Result
Uguralp *et al.* (2004)	Cold stress induced NEC in rats	INF-α	↓Severity of NEC
Ozdemir *et al.* (2012)	Cold stress/hypoxia-hyperoxia induced NEC in rats	NAC	Protective effect on intestinal injury
Tayman *et al.* (2012)	Cold stress/hypoxia-hyperoxia induced NEC in rats	NAC	↓Severity of bowel damage; ↓MDA, MPO, XO; ↑TAS
Zani *et al.* (2008)	Hypertonic formula/hypoxia /oral LPS induced NEC in rats	Captopril	↓Severity of bowel damage; ↓Mesenteric ischemia
Feng *et al.* (2006a,b)	Cold stress/hypertonic formula/hypoxia /oral LPS induced NEC in rats	HB-EGF	↓Incidence & severity of NEC; ↓Apoptosis
Cadir *et al.* (2008)	Hypoxia-reoxygenation induced NEC in rats	Omeprazol/vitamin E	↓Severity of histopathological damage in intestine
Guven *et al.* (2009b)	Cold stress/hypoxia induced NEC in rats	HBO therapy	↓Severity of inflammation in NEC
Guven *et al.* (2011)	Cold stress/hypoxia induced NEC in rats	Melatonin	↓Severity of NEC
Guven *et al.* (2009a)	Cold stress/hypoxia induced NEC in rats	Ozone	↓Severity of inflammation in NEC
Okur *et al.* (1995)	Hypoxia-reoxygenation induced NEC in rats	Vitamin E	↓Severity of NEC

HB-EGF: Heparin-binding epidermal growth factor-like growth factor, HBO: Hyper baric oxygen, INF: Interferon, LBS: Lipopolysaccharide, MDA: Malondialdehyde, MPO: Myeloperoxidase,NAC: Acetylcysteine, NEC: Necrotizing enterocolitis, TAS: Total antioxidant status and XO: Xanthine oxidase

Table 2: Details of experimental studies using Ptx for treatment of NEC

Study	Model	Results
Hammerman *et al.* (1999)	Intestinal IR induced NEC in rats	↓Histopathologic signs of injury; ↓TBARS
Travadi *et al.* (2006)	Cold stress/hypoxia induced NEC in rats	↓Severity of NEC
Erdener *et al.* (2004)	Hypoxia- reperfusion induced NEC in rabbits	No protective effect on NEC

IR: Ischemia reperfusion, NEC: Necrotizing enterocolitis, Ptx: Pentoxifylline, TBARS: Lipid peroxidation, XO: Xanthine oxidase

included different phases of hypoxy-reoxygenation, cold stress and/or lipopolysaccharide administration besides the enteral formula feeding. Consequently, the similar inflammatory condition in NEC occurs by lipid peroxidation injury and free radical release (Rezaie *et al.*, 2007). In consideration of acquiring the main mediators and essential therapeutic targets, different interventions have been evaluated in NEC models. There are a substantial focus on substances with anti-oxidant activities such as N-acetylcysteine, vitamin E, omeprazole and hyperbaric oxygen (HBO. The results demonstrated that anti-oxidant therapy had protective effect on the intestinal injury and is able to diminish the severity of bowel damage in NEC. This beneficial effect was through inhibition of free radical formation (vitamin E, omeprazole) (Okur *et al.*, 1995; Cadir *et al.*, 2008), reduction of xanthine oxidase, malondialdehyde (MDA) levels and myeloperoxidase activity in addition to increase in total anti-oxidant status (N-acetylcysteine) (Ozdemir *et al.*, 2012; Tayman *et al.*, 2012) and improvement of white blood cell actions besides angiogenesis effects (HBO therapy) (Guven *et al.*, 2009b). Some investigated treatments exhibited both anti-oxidant effect and anti-inflammatory protection like melatonin (Guven *et al.*, 2011) and ozone therapy (Guven *et al.*, 2009a). In addition, INF-alpha showed a modulator effect on cytokines resulting in reduction of the severity of NEC damage (Uguralp *et al.*, 2004). Heparin-binding epidermal growth factor-like growth factor (HB-EGF) has been evaluated by Feng *et al.* (2006a, b) that showed preservation of gut barrier integrity and reduction of apoptosis. Furthermore, captopril reduced the mesenteric ischemia via inhibition of rennin-angiotensin system during shock (Zani *et al.*, 2008).

DISCUSSION

NEC is known as one of the causes of death in neonate intensive care units that is prevalent in premature newborns. Prematurity, alteration in gastrointestinal microbial flora or infection, history of use of broad spectrum antibiotics, enteral feeding and sepsis are among proposed pathophysiologies (Luedtke *et al.*, 2012; Hsueh *et al.*, 2003). The maternal breast milk and conservative feeding practices are suggested as one of preventive factors to reduce NEC prevalence by influencing the colonization of microbial flora (Luedtke *et al.*, 2012). Amongst investigated substances, Ptx may be of great interest based on results of experimental studies (Table 2) and due to its beneficial potentials for NEC management. Nevertheless, the safety profile of Ptx should be noted especially when used in combination with other drugs in the management of sepsis in neonates. Haque and Pammi (2003; 2011) showed that Ptx in combination with antibiotics reduces the mortality in affected infants with sepsis without leaving any adverse effects. Ptx does not result in any cardiac or bronchodilatory side effects when used in therapeutic doses (Harris *et al.*, 2010). It caused no thrombocytopenia and bleeding in infants with sepsis or NEC (Harris *et al.*, 2010). Additionally, Downard *et al.* (2012) investigated the direct peritoneal resuscitation method in an animal model of NEC. They suggested that this method could be effective in improving the blood flow in the bowel of affected animals. Thus, Ptx has the potential to preserve microvascular blood flow and can be considered as a preference in management of NEC. Collectively, further controlled clinical trials should be established to confirm the beneficial preventive and/or

therapeutic use of Ptx in NEC, considering its safety issues in neonates as current evidences are mostly based on experimental reports and no clinical trial has been performed in NEC yet.

ACKNOWLEDGMENTS

This study is the outcome of an in-house financially non-supported study. Authors thank help of National Elite Foundation and Iran National Science Foundation (INSF).

REFERENCES

Arciero, J., G.B. Ermentrout, R. Siggers, A. Afrazi, D. Hackam, Y. Vodovotz and J. Rubin, 2013. Modeling the interactions of bacteria and Toll-like receptor-mediated inflammation in necrotizing enterocolitis. J. Theor. Biol., 321: 83-99.

Badri, S., S. Dashti-Khavidaki, M. Lessan-Pezeshki and M. Abdollahi, 2011. A review of the potential benefits of pentoxifylline in diabetic and non-diabetic proteinuria. J. Pharm. Pharm. Sci., 14: 128-137.

Cadir, F.O., U. Bicakci, B. Tander, B. Kilicoglu-Aydin and R. Rizalar *et al*., 2008. Protective effects of vitamin E and omeprazole on the hypoxia/reoxygenation induced intestinal injury in newborn rats. Pediatr. Surg. Int., 24: 809-813.

Caplan, M.S., X.M. Sun and W. Hsueh, 1990. Hypoxia causes ischemic bowel necrosis in rats: The role of platelet-activating factor (PAF-acether). Gastroenterology, 99: 979-986.

Ciuffetti, G., M. Mercuri, C. Ott, R. Lombardini and R. Paltriccia *et al*., 1991. Use of pentoxifylline as an inhibitor of free radical generation in peripheral vascular disease. Eur. J. Clin. Pharmacol., 41: 511-515.

Claud, E.C., 2012. First do no harm. J. Pediatr. Pharmacol. Ther., 17: 298-301.

Downard, C.D., P.J. Matheson, J.A. Shepherd, A.C. Maki and R.N. Garrison, 2012. Direct peritoneal resuscitation augments ileal blood flow in necrotizing enterocolitis via a novel mechanism. J. Pediatr. Surg., 47: 1128-1134.

Erdener, D., F. Bakirtas, M. Alkanat, I. Mutaf, S. Habif and O. Bayindir, 2004. Pentoxifylline does not prevent hypoxia/reoxygenation-induced necrotizing enterocolitis. Biol. Neonate, 86: 29-33.

Ergun, O., G. Ergun, G. Oktem, N. Selvi and H. Dogan *et al*., 2007. Enteral resveratrol supplementation attenuates intestinal epithelial inducible nitric oxide synthase activity and mucosal damage in experimental necrotizing enterocolitis. J. Pediatr. Surg., 42: 1687-1694.

Feng, J., O.N. El-Assal and G.E. Besner, 2006a. Heparin-binding epidermal growth factor-like growth factor decreases the incidence of necrotizing enterocolitis in neonatal rats. J. Pediatr. Surg., 41: 144-149.

Feng, J., O.N. El-Assal and G.E. Besner, 2006b. Heparin-binding epidermal growth factor-like growth factor reduces intestinal apoptosis in neonatal rats with necrotizing enterocolitis. J. Pediatric Surgery, 41: 742-747.

Freitas, J.P. and P.M. Filipe, 1995. Pentoxifylline: A hydroxyl radical scavenger. Biol. Trace Element Res., 47: 307-311.

Ghiasi, S., S. Ghiasi and M. Abdollahi, 2012. A review on the potential benefits of phosphodiesterase inhibitors in various models of toxicities in animals. Asian J. Anim. Vet. Adv., 7: 210-224.

Guven, A., G. Gundogdu, B. Uysal, H. Cermik and M. Kul *et al*., 2009a. Hyperbaric oxygen therapy reduces the severity of necrotizing enterocolitis in a neonatal rat model. J. Pediatric Surgery, 44: 534-540.

Guven, A., G. Gundogdu, S. Vurucu, B. Uysal, E. Oztas, H. Ozturk and A. Korkmaz, 2009b. Medical ozone therapy reduces oxidative stress and intestinal damage in an experimental model of necrotizing enterocolitis in neonatal rats. J. Pediatric Surgery, 44: 1730-1735.

Guven, A., B. Uysal, G. Gundogdu, E. Oztas, H. Ozturk and A. Korkmaz, 2011. Melatonin ameliorates necrotizing enterocolitis in a neonatal rat model. J. Pediatric Surgery, 46: 2101-2107.

Hammerman, C., D. Goldschmidt, M.S. Caplan, M. Kaplan and M.S. Schimmel *et al*., 1999. Amelioration of ischemia-reperfusion injury in rat intestine by pentoxifylline-mediated inhibition of xanthine oxidase. J. Pediatric Gastroenterol. Nutr., 29: 69-74.

Haque, K.N. and M. Pammi, 2003. Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. Cochrane Library. 10.1002/14651858.CD004205

Haque, K.N. and M. Pammi, 2011. Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. Cochrane Library 10.1002/14651858.CD004205.pub2

Harpavat, S., M. Pammi and M. Gilger, 2012. Novel treatments for NEC: Keeping IBD in mind. Curr. Gastroenterol. Rep., 14: 373-379.

Harris, E., S.M. Schulzke and S.K. Patole, 2010. Pentoxifylline in preterm neonates: A systematic review. Paediatr. Drugs, 12: 301-311.

Hsueh, W., M.S. Caplan, X.W. Qu, X.D. Tan, I.G. De Plaen ande F. Gonzalez-Crussi, 2003. Neonatal necrotizing enterocolitis: Clinical considerations and pathogenetic concepts. Pediatr. Dev. Pathol., 6: 6-23.

Khoshakhlagh, P., M. Bahrololoumi-Shapourabadi, A. Mohammadirad, L. Ashtaral-Nakhai, B. Minaie and M. Abdollahi, 2007. Beneficial effect of phosphodiesterase-5 inhibitor in experimental inflammatory bowel disease: Molecular evidence for involvement of oxidative stress. Toxicol. Mech. Methods, 17: 281-288.

Lauterbach, R. and M. Zembala, 1996. Pentoxifylline reduces plasma tumour necrosis factor-alpha concentration in premature infants with sepsis. Eur. J. Pediatr., 155: 404-409.

Lauterbach, R., D. Pawlik, D. Kowalczyk, W. Ksycinski, E. Helwich and M. Zembala, 1999. Effect of the immunomodulating agent, pentoxifylline, in the treatment of sepsis in prematurely delivered infants: A placebo-controlled, double-blind trial. Crit. Care Med., 27: 807-814.

Lin, P.W. and B.J. Stoll, 2006. Necrotising enterocolitis. Lancet, 368: 1271-1283.

Luedtke, S.A., J.T. Yang and H.E. Wild, 2012. Probiotics and necrotizing enterocolitis: Finding the missing pieces of the probiotic puzzle. J. Pediatr. Pharmacol. Ther., 17: 308-328.

Okur, H., M. Kucukaydin, K. Kose, O. Kontas, P. Doan and A. Kazez, 1995. Hypoxia-induced necrotizing enterocolitis in the immature rat: The role of lipid peroxidation and management by vitamin E. J. Paediatr. Surg., 30: 1416-1419.

Ozdemir, R., S. Yurttutan, F.N. Sari, B. Uysal and H.G. Unverdi *et al*., 2012. Antioxidant effects of N-acetylcysteine in a neonatal rat model of necrotizing enterocolitis. J. Pediatr. Surg., 47: 1652-1657.

Parks, D.A. and D.N. Granger, 1983. Ischemia-induced vascular changes: Role of xanthine oxidase and hydroxyl radicals. Am. J. Physiol. Gastrointestinal Liver Physiol., 245: G285-G289.

Patole, S., 2007. Prevention and treatment of necrotising enterocolitis in preterm neonates. Early Hum. Dev., 83: 635-642.

Rahimi, R., S. Ghiasi, H. Azimi, S. Fakhari and M. Abdollahi, 2010. A review of the herbal phosphodiesterase inhibitors: Future perspective of new drugs. Cytokine, 49: 123-129.

Rezaie, A., R.D. Parker and M. Abdollahi, 2007. Oxidative stress and pathogenesis of inflammatory bowel disease: An epiphenomenon or the cause. Dig. Dis. Sci., 52: 2015-2021.

Rezvanfar, M.A., H.R. Rahimi and M. Abdollahi, 2012. ADMET Considerations for Phosphodiesterase-5 Inhibitors. Expert Opin. Drug Metab. Toxicol., 8: 1231-1245.

Salari, P. and M. Abdollahi, 2012. Phosphodiesterase inhibitors in inflammatory bowel disease. Expert. Opin. Investig. Drugs., 21: 261-264.

Salari-Sharif, P. and M. Abdollahi, 2010. Phosphodiesterase 4 inhibitors in inflammatory bowel disease: A comprehensive review. Curr. Pharm. Des., 16: 3661-3667.

Shah, D. and J.K. Sinn, 2012. Antibiotic regimens for the empirical treatment of newborn infants with necrotising enterocolitis. Cochrane. Database. Syst. Rev., Vol. 8. 10.1002/14651858.CD007448.pub2

Tayman, C., A. Tonbul, A. Kosus, I.M. Hirfanoglu and S. Uysal *et al*., 2012. N-acetylcysteine may prevent severe intestinal damage in necrotizing enterocolitis. J. Pediatr. Surg., 47: 540-550.

Travadi, J., S. Patole, A. Charles, B. Dvorak, D. Doherty and K. Simmer, 2006. Pentoxifylline reduces the incidence and severity of necrotizing enterocolitis in a neonatal rat model. Pediatr. Res., 60: 185-189.

Uguralp, S., B. Mizrak, A.B. Karabulut, N. Gurbuz and M. Demircan, 2004. Interferon-alpha reduces the development of experimental necrotizing enterocolitis. Cytokine, 25: 204-211.

Zani, A., S. Eaton, F.F. Leon, A. Malerba and N.J. Hall *et al*., 2008. Captopril reduces the severity of bowel damage in a neonatal rat model of necrotizing enterocolitis. J. Pediatr. Surg., 43: 308-314.