TANG [HUMANITAS MEDICINE]

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Review

Suppression of nitric oxide (NO) production by traditional medicine

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ABSTRACT

Nitric oxide (NO) is a small diffusible molecule which plays an important role in various physiological activities. NO is a notable molecule, functioning as a cytotoxic agent and cellular messenger. There has been considerable interest in NO production by activated macrophages because this gaseous metabolite plays a fundamental role in the cytotoxic and cytostatic effects of macrophages towards invasive micro-organisms and tumour cells. No is a bioactive free radical that has been implicated in many physiological functions, plays a critical role during inflammation and therefore constitutes a potential target for developing therapeutics for inflammatory diseases. The use of medicinal plants by the population has been an important alternative the resource in the treatment of various diseases. Its growing acceptance in the medical community has been due to the fact that several plants with biological activities have been scientifically investigated and their efficacy and safety have been proven. In this review, discussed suppressive effects of No production by traditional medicines in RAW 264.7 and THP-1 macrophages.

Keywords nitric oxide, RAW 264.7 macrophages, THP-1 macrophages, traditional medicines

INTRODUCTION

Monocytes and macrophages belong to the innate immune compartment in which their major roles are recognition of foreign pathogens such as bacteria, fungi and viruses via interaction of their surface structures with different types of Pattern Recognition Receptors (PRRs), proliferation to increase the amount of cells that are able to eliminate pathogens, production of pro-inflammatory chemokines and cytokines (Tahar et al., 2009).

The World Health Organization (WHO) defines Traditional Medicine as “the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses” (WHO, 2014). TM practices, particularly comprehensive medical systems such as traditional Chinese Medicine and Ayurveda, share many of the same core values (Bell, 2001). Plant has long been used clinically as an anti-inflammatory drug. Plants contain a wide variety of microcomponents, including enzyme inhibitors, phytosterols, indoles, flavones, and saponins. Many of these microcomponents are biologically active and role in the prophylaxy of chronic diseases is being investigated at the present time (Agarwal and Rao, 2000; Brandi, 1997; Craig, 1999; Larner, 1995). They are widely studied about versatile biological activities, such as cytotoxic, anti-inflammatory, immunosuppressive antitumor and antifeedant activities As part of our ongoing search for anti-inflammatory compounds from plants the major traditional medicines from the anti-inflammatory of plant isolated, identified, and their inhibitory effects on overexpression of inflammatory mediators including nitric oxide (NO) was examined in RAW264.7 and THP-1 macrophages.

RAW 264.7 macrophages

The RAW 264.7 male mouse macrophage cell line was formulate a tumor derived by Abelson murine leukemia virus (MuLV). RAW 264.7 macrophages are negative for surface antigens surface Ia and Thy-1 2 and immunoglobulin. RAW 264.7 line was reported not to secrete a detectable amount of virus. However, unpublished data showed that Janet W. Hartley's expression of the infectious Ecotropic Abelson MuLV was not closely related to the Moloney MuLV helper virus employ in the circular virus vaccine. RAW 264.7 macrophages are capable of antibody dependant lysis of tumor cell targets and sheep erythrocytes. Lipopolysaccharide or p-Phenylenediamine treatment for two days stimulates lysis of erythrocytes but not tumor cell targets. It is of note that RAW 264.7 macrophages are no monocytes but dividing macrophages (Lorkowski, 201; Ralph and Nakoinz, 1977).

In recent years, the cell line has also been used extensively in proteomics experiments including a large-scale proteome (Raschke et al., 1978), phagosome proteomics (Boulais et al., 2012; Campbell-Valois et al., 2012; Trost et al., 2009) responses to cytokines (Bell et al., 2013; Marcantonio et al., 2008) and identification of DNA receptors (Burckstummer et al., 2009).

THP-1 macrophages

The THP-1 cell line was isolated from the blood of a 1 year old,

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likely acute monocytic leukemia. These monocytes have C3b and Fc receptors, but no cytoplasmic immunoglobulins or surface. HLA haploid genotype of THP-1 cells are HLA-A2, -B5, -A9, -DRW2 and -DRW1. THP-1 cells don't possess Epstein Barr virus owned nuclear antigen (Tsuchiya et al., 1980). Monocytic differentiation of THP-1 cells can be derived use phorbol esters like phorbol-12-myristate-13-acetate. After four days of phorbol ester treatment, THP-1 cells are matured into macrophages. (Lorkowski, 2011). In contrast to native human monocytes, a cell line such as THP-1 offers the additional advantage of a homogeneous population, which markedly facilitates further biochemical study. THP-1 cell line has been widely use to study immune responses while cells are not only in the monocyte state but also in the macrophage-like state. (Daigneault et al., 2010; Schwende et al., 1996).

NO production in the immune system

NO is a small diffusible molecule which plays an important role in various physiological activities (Icerwin Jr, 1995) it is synthesised from L-arginine by nitric oxide synthase (NOS). Three distinct types of this enzyme have been identified: endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS) (Nathan and Xie, 1994). eNOS and , nNOS are constitutively expressed and their activity are Ca^{2+} / calmodulim-dependent. iNOS is functionally Ca^{2+} / calmodulim independent and it synthesises large amounts of NO from macrophages (Stuehr, 1991), neutrophils and microglial cells (Chao et al., 1992) when these cells are induced by endotoxin or cytokines. NO is a remarkable molecule, functioning as a cellular messenger and cytotoxic agent. This short-lived mediator is formed by the sequential oxidation of the substrate L-arginine by the NO synthase (NOS) family of enzymes, with the formation of L-citrulline and NO as the byproduct (Nathan, 1992) NO has been implicated in numerous homeostatic functions, including vasodilation (Palmer et al., 1987), neurotransmission (Bredt et al., 1992) and host defense against pathogens (Nathan and Hibbs, 1991) and also in pathological conditions, such as sepsis, autoimmune diseases, asthma, and other inflammatory diseases (Christopherson et al., 1997; Curran , 1996; Yeadon et al., 1995). There has been considerable interest in NO production by activated macrophages because this gaseous metabolite plays a fundamental role in the cytotoxic and cytostatic effects of macrophages towards invasive micro-organisms and tumour cells (Langrehr et al., 1993). NO has also been implicated in the pathogeneais of various immunologically-mediated diseases such as septic shock and rheumatoid arthritis (Vallance et al., 1991; Farrell et al., 1992). Many agonists which are able to induce iNOS in macrophages have been identified and among them, LPS and some cytokines such as interferon y (INF-y) are the most characterised (Gross et al., 1991). NO is synthesised from L-arginine by nitric although this basic definition is still accepted, during the past decade it has been recognized that NO plays many more roles in the immune system (Bogdan, 2000). First, in addition to macrophages (MacMicking et al., 1997; Nathan and Hibbs, 1991), a large number of other immune-system cells produce and respond to NO. It exhibits an astonishing range of physiologic functions, from immune defense to blood pressure regulation to the inhibition of platelet aggregation (Bogdan, 2000; Lowenstein et al., 1994). NO is synthesized from the amino acid L-arginine by a family of enzymes, the NOS, through a metabolic route known as the L-arginine NO pathway (Moncada and Higgs, 1993; Moncada et al., 1989). NO has a short life in aqueous and oxygen-containing solutions (Moncada et al., 1991).

Macrophages participate actively in the inflammatory response by releasing cytokines, chemokines and factors that recruit additional cells to sites of infection or tissue injury or alteration. Expletively, activated macrophages immediately activate the expression of genes accountable for the high-power synthesis of nitrogen species (NO, O^{2-}, H_2O_2 and peroxynitrite, among others), reactive oxygen and bioactive lipids derived from arachidonic acid.

Table 1. An inhibitory effect of traditional medicines on NO production

Cell	Traditional medicines	Reference
Raw 264.7	*Lilium brownii var. viridulum*	Ma et al., 2017
Raw 264.7	*Euphorbia supina*	Chae et al., 2014
Raw 264.7	*Physalis minima*	Li et al., 2017
Raw 264.7	*Panax ginseng*	Jang et al., 2016
Raw 264.7	*Cyperus rotundus*	Seo et al., 2016
Raw 264.7	*Alfalfa*	Choi et al., 2013
Raw 264.7	*Aurea helianthus*	Kim et al., 2017
Raw 264.7	*blackberry wine*	Caillot et al., 2018
Raw 264.7	*Parinari curatellifolia*	Gororo et al 2016
Raw 264.7	*Humulus japonicus*	Lim et al., 2016
Raw 264.7	*Taraxacum officinale Weber*	Park et al., 2011
Raw 264.7	*Citrus reticulata*	Jung et al., 2007
Raw 264.7	*Annona muricata*	Kim et al., 2016
Raw 264.7	*Dendropanax morbifera Leveille*	Akram et al., 2016
Raw 264.7	*Portulaca oleracea L.*	Meng et al., 2016
Raw 264.7	*Angelica decursiva*	Ishita et al., 2016
Raw 264.7	*Fragaria vesca*	Liberal et al., 2014
THP-1	*Hypericum triquetrifolium*	Saad et al., 2011
THP-1	*Armillariella mellea*	Wu et al., 2007

All of these agents contribute to the regulation of the inflammatory response (Bosca, 2005). The overproduction of inflammatory mediators is closely associated with the pathogenesis of inflammation. Thus, suppression of inflammatory mediators is considered a promising therapeutic strategy for various inflammatory diseases (Charo et al., 2006).

Anti-inflammatory effects of traditional medicines

Many drugs are presently prescribed all over the world for the management of inflammation-related disorders. But there is a problem with this drugs. Use of these agents is finite due to the leading issues of cardiovascular problems, elevated blood pressure, kidney damage and gastrointestinal damage (Burke et al., 2006; Scheiman, 2001; Wolfe et al., 1999). Thus, over the past several decades, many researchers have focused on medicinal plants with few side effects in an effort to develop anti-inflammatory and analgesic drugs. No is a bioactive free radical that has been implicated in many physiological functions, plays a critical role during inflammation and therefore constitutes a potential target for developing therapeutics for inflammatory diseases (Hofseth, 2008). Macrophages are immune cells implicated in the initiation of inflammatory responses, secreting several pro-inflammatory mediators, including NO and pro-inflammatory cytokines, like tumor necrosis factor (TNF-α) and interleukin 1-β (IL-1β). (Lee and Park, 2015). NO production is considered to be related to the pathogenesis of several diseases such as inflammation and NO is a major inflammatory mediator involved in various inflammatory diseases. In this study, the inhibitory activity of NO production was used to guide the isolation of fractions and compounds responsible for the anti-inflammatory effect from traditional medicines. Therefore, NO may be a useful therapeutic target for mast cell-mediated inflammatory diseases. Based on the inhibitory effect of NO production reported, drugs were shown in Table 1.

CONCLUSION

The use of medicinal plants by the population has been an important alternative the rapeutic resource in the treatment of various diseases. Its growing acceptance in the medical commu nity has been due to the fact that several plants with biological activities have been scientifically investigated and their efficacy and safety have been proven (Abdelmigid, 2013; Jordan et al., 2010). Recently, greater attention has been focused on the use of plants and plant-derived components due to their anti-inflammatory efficacy, which results from their multi-component features including the ability to affect multiple targets and levels of signaling pathways and their multiple mechanisms of mitigating inflammation (Drayton et al., 2006). In this study Anti-inflammatory substance were extracted used each extraction method in traditional medicines and showed that NO production were reduced in RAW 264.7 and THP-1 macrophages after treatment to anti-inflammatory substance. These results suggest that traditional medicines reduce inflammation by reducing the NO production and would be an active ingredient in potential treatment for inflammatory diseases. That traditional medicines can be a potential source of medicines for inflammatory diseases.

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CONFLICT OF INTEREST

The authors have no conflicting financial interests.

REFERENCES

Abdelmigid HM. New trends in genotoxicity testing of herbal medicinal plants. In New Insights into Toxicity and Drug Testing. Sivakumar Gowder ed. 5th ed. (Rijeka, Croatia: Intech), pp. 89-120, 2013.

Agarwal S, Rao AV. Carotenoids and chronic diseases. Drug Metabol Drug Interact. 2000;17;189–210.

Akram M, Kim KA, Kim ES, Syed AS, Kim CY, Lee J S, Bae ON. Potent Anti-inflammatory and Analgesic Actions of the Chloroform Extract of Dendropanax morbifera Mediated by the Nrf_2/HO^{-1} Pathway. Biol Pharm Bull. 2016;39:728–736.

Bell C, Boulais L, Boulais J, Chemali M, Caron-Lizotte O, Desjardins M, Thibault P. Quantitative proteomics reveals the induction of mitophagy in tumor necrosis factor-alpha-activated (TNFalpha) macrophages. Mol Cell Proteomics. 2013;12:2394–2407.

Bell IR. Integrative medicine and systemic outcomes research. Arch Intern Med. 2002;162:133–140.

Bogdan C, Rollinghoff M, Diefenbach A. The role of nitric oxide in innate immunity. Immunol Rev. 2000;173:17–26.

Bosca L, Zeinia M, Traves PG, Hortelano S. Nitric oxide and cell viability in inflammatory cells: a role for NO in macrophage function and fate. Toxicology. 2005;208:249–258

Boulais J, Trost M, Landry CR, Dieckmann R. Molecular characterization of the evolution of phagosomes. Mol Syst Biol. 2010;6:423.

Brandi ML. Natural and synthetic isoflavones in the prevention and treatment of chronic diseases. Calcif Tissue Int. 1997;61:5–8.

Bredt DS, Snyder SH. Nitric oxide a novel neuronal messenger. Neuron. 1992;8:3–11.

Burckstummer T, Baumann C, Bluml S, Dixit E. An orthogonal proteomic-genomic screen identifies AIM2 as a cytoplasmic DNA sensor for the inflammasome. Nat Immunol. 2009;10:266–272.

Burke A, Smyth E, Fitzgerald GA. Analgesic antipyretic agents: pharmacotherapy of gout. In The Pharmacological Basis of Therapeutics. Brunton LL, Lazo JS, Parker KL ed.11th ed. (New York, USA: McGraw Hill Company Incorporation), pp. 706, 2006.

Caillot ARC, Bezerra IdL, Palhares LCGF, Santana-Filho AP, Chavante SF, Sassaki GL. Structural characterization of blackberry wine polysaccharides and immunomodulatory effects on LPS-activated RAW 264.7 macrophages. Food Chem. 2018;257:143–149.

Campbell Valois FX, Trost M, Chemali M, Dill BD, Laplante A, Duclos S, Sadeghi S, Rondeau C, Morrow IC, Bell C, Gagnon E, Hatsuzawa K, Thibault P, Desjardins M. Quantitative proteomics reveals that only a subset of the endoplasmic reticulum contributes to the phagosome. Mol Cell Proteomics. 2012:11;M111 016378.

Chae HS, Kim YM, Lee EJ, Song HH, Oh SR, Choi YH, Chin YW. Corilagin with Inhibitory Activity against NO Production from Euphorbia supina. Natural Product Sciences.

2014;20:126-129.

Chao CC, Hu S, Molitor TW, Shaskan EG, Peterson PK. Activated microglia mediate neuronal cell injury via a nitric oxide mechanism. J Immunol. 1992;149:2736-2741.

Charo IF, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med. 2006;354:610–621.

Choi KC, Hwang JM, Bang SJ, Kim BT, Kim DH, Chae M, Lee SA, Choi GJ, Kim DH, Lee JC. Chloroform extract of Alfalfa (Medicago sativa) inhibits lipopolysaccharide-induced inflammation by downregulating ERK/NF-κB signaling and cytokine Production. J Med Food. 2013;16:410–420.

Christopherson KS, Bredt DS. Nitric oxide in excitable tissues: physiological roles and disease. J Clin Investig. 1997;100:2424-2429.

Craig WJ. Health-promoting properties of common herbs. Am J Clin Nut. 1999;70:491-499.

Curran AD. The role of nitric oxide in the development of asthma. Int. Arch. Allergy Immunol. 1996;111:1-4.

Daigneault M, Preston JA, Marriott HM, Whyte MK, Dockrell DH. The identification of markers of macrophage differentiation in PMA-stimulated THP-1 cells and monocyte-derived macrophages. PLoS One. 2010;5:e8668.

Drayton DL, Liao S, Mounzer RH, Ruddle NH. Lymphoid organ development: from ontogeny to neogenesis. Nat Immunol. 2006;7:344–353.

Farrell AJ, Blake DR, Palmer RM, Moncada S. Increased concentrations of nitrite in synovial fluid and serum samples suggest increased nitric oxide synthesis in rheumatic diseases. Ann Rheum Dis. 1992;51:1219-1222.

Gororo M, Chimponda T, Chirisa E, Mukanganyama S. Multiple cellular effects of leaf extracts from Parinari curatellifolia. BMC Complement Altern Med. 2016;16:305.

Gross SS, Jaffe EA, Levi R, Rilbourn RG. Cytokine activated endothelial cells express an isotype of nitric oxide synthase which is tetrahydrobiopterin dependent calmodulin independent and inhibited by arginine analogs with a rank order of potency characteristic of activated macrophages. Biochem Biophys Res Commuu. 1991;178:823-829.

Hofseth LJ. Nitric oxide as a target of complementary and alternative medicines to prevent and treat inflammation and cancer. Cancer Lett. 2008;268:10-30.

Icerwin Jr JF, Lancaster Jr JR, Feldman PL. Nitric Oxide: A New Paradigm for Second Messengers. J Med Chem. 1995;28:4343-4362.

Ishita IJ, Islam MN, Kim YS, Choi RJ, Sohn HS, Jung HA, Choi JS. Coumarins from Angelica decursiva inhibit lipopolysaccharide induced nitrite oxide production in RAW 264.7 cells. Arch Pharm Res. 2016;39:115–126.

Jang KJ, Choi SH, Yu GJ, Hong SH, Chung YH, Kim CH, Yoon HM, Kim GY, Kin BW, Choi TH. Anti-inflammatory potential of total saponins derived from the roots of Panax ginseng in lipopolysaccharide activated RAW 264.7 macrophages. Exp Ther Med. 2016;11:1109-1115.

Jordan SA, Cunningham DG, Marles RJ. Assessment of herbal medicinal products: challenges and opportunities to increase the knowledge base for safety assessment. Toxicol Appl Pharmacol. 2010;243:198-216.

Jung KH, Ha EY, Kim MJ, Won HJ, Zheng LT, Kim HK, Hong SJ, Chung JH, Yim SV. Suppressive effects of nitric oxide (NO) production and inducible nitric oxide synthase (iNOS) expression by Citrus reticulate extract in RAW 264.7 macrophage cells. Food Chem Toxicol. 2007;45:1545–1550.

Kim GT, Tran NKS, Choi EH, Song YJ, Song JH, Shim SM, Park TS. Immunomodulatory Efficacy of Standardized Annona muricata (Graviola) Leaf Extract via Activation of Mitogen-Activated Protein Kinase Pathways in RAW 264.7 Macrophages. Evid Based Complement Alternat Med. 2016;1:10

Kim HJ, Park CG, Varghese R, Lee JY, Kim YO, Sung GH. In-vitro anti-oxidative, anti-inflammatory properties of Aurea helianthus leaf extract a Korean traditional medicinal plant. Saudi J Biol Sci. 2017;24:1943-1947.

Kroncke KD, Fehsel K, Kolb Bachofen V. Inducible nitric oxide synthase in human diseases. Clin and Exp Immunol. 1998;113:147–156.

Langrehr JM, Hoffman RA, Lancaster JR, Simmons RL. Nitric oxide a new endogenous immunomodulator. Transplantation. 1993;55:1205-1212.

Larner AJ. How does garlic exert its hypocholesterolaemic action? The tellurium hypothesis. Med Hypotheses. 1995;44:295–297.

Lee JY, Park W. Anti-Inflammatory effect of wogonin on RAW 264.7 mouse macrophages induced with polyinosinic polycytidylic acid. Molecules. 2015;20:6888–6900.

Liberal J, Francisco V, Costa G, Figueirinha A, Amaral MT, Marques C, Girão H, Lopes MC, Cruz MT, Batista MT. Bioactivity of Fragaria vesca leaves through inflammation proteasome and autophagy modulation. J Ethnopharmacol. 2014;58:113–122.

Lim H, Noh JR, Kim YH, Hwan JH, Kim KS, Choi DH, Go MJ, Han SS, Oh KW, Lee CH. Anti-atherogenic effect of Humulus japonicus in apolipoprotein E deficient mice. Int j mol med. 2016;38:1101-1110.

Li RJ, Gao CY, Guo C, Zhou MM, Luo J, Kong LY. The Anti inflammatory Activities of Two Major With anolides from Physalis minima Via Acting on NF-κB, STAT3, and HO^{-1} in LPS-Stimulated RAW264.7 Cells. Inflammation. 2017;40:401–413.

Lorkowski S. Monocytic and macrophage-like cell lines. 2011. Available at:
http://www.infarktforschung.de/macrophages_cell_lines.html. (accessed on 01th May 2018).

Lowenstein CJ, Dinerman JL, Snyder SH. Nitric oxide: a

physiologic messenger. Ann Int Med. 1994;120:227–237.

MacMicking J, Xie QW, Nathan C. Nitric oxide and macrophage function. Annu Rev Immunol. 1997;15:323–350.

Marcantonio M, Trost M, Courcelles M, Desjardins M, Thibault P. Combined enzymatic and data mining approaches for comprehensive phosphoproteome analyses: application to cell signaling events of interferon-gamma- stimulated macrophages. Mol Cell Proteomics. 2008;7:645–660.

Ma T, Wang Z, Zhang YM, Luo JG, Kong LY. Bioassay-Guided Isolation of Anti-Inflammatory Components from the Bulbs of Lilium brownii var. viridulum and Identifying the Underlying Mechanism through Acting on the NF-κB/MAPKs Pathway. Molecules. 2017;22:506-523.

Meng Y, Ying Z Xiang Z, Hao D Zhang W, Zheng Y, Gao Y, Ying X. The anti inflammation and pharmacokinetics of a novel alkaloid from Portulaca oleracea L. J Pharm Pharmacol. 2016;68:397-405.

Moncada S, Higgs A. The L arginine nitric oxide pathway. New Engl J Med. 1993;329:2002-2012.

Moncada S, Palmer RMJ, Higgs EA. Biosynthesis of nitric oxide from L-arginine. A pathway for the regulation of cell function and communication. Biochem Pharmacol. 1989;38:1709–1715.

Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology and pharmacology. Pharmacol Rev. 1991;43:109–142.

Mordan LJ, Burnett TS, Zhang LX. Inhibitors of endogenous nitrogen oxide formation block the promotion of neoplastic transformation in $C_3H_{10}T1/2$ fibroblasts. Carcinogenesis. 1993;14:1555–1559.

Nathan C. Nitric oxide as a secretory product of mammalian cells. Faseb J. 1992;6:3051–3064.

Nathan CF, Hibbs JB. Role of nitric oxide synthesis in macrophage antimicrobial activity. Curr Opin Immunol. 1991;3:65–70.

Nathan CF, Xie QW. Regulation of biosynthesis of nitric oxide. J Biol Chem. 1994;269:13725-13728.

Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature. 1987;327:524–526.

Park CM, Park JY, Noh KH, Shin JH, Song YS. Taraxacum officinale Weber extracts inhibit LPS-induced oxidative stress and nitric oxide production via the NF-κB modulation in RAW 264.7 cells. J Ethnopharmacol. 2011;27:834-842.

Ralph P, Nakoinz I. Antibody dependent killing of erythrocyte and tumor targets by macrophage related cell lines: enhancement by PPD and LPS. J Immunol. 1977;119(3):950-954.

Raschke WC, Baird S, Ralph P, Nakoinz I. Functional macrophage cell lines transformed by Abelson leukemia virus. Cell. 1978;15:261–267.

Ritorto MS, Cook K, Tyagi K, Pe drioli PG, Trost M. Hydrophilic strong anion exchange (hSAX) chromatography for highly orthogonal peptide separation of complex proteomes. J Proteome Res. 2013;12:2449–2457.

Saad B, Abouatta BS, Basha W, Hmade A, Kmail A, Khasib S, Said O. Hypericum triquetrifolium Derived Factors Downregulate the Production Levels of LPS-Induced Nitric Oxide and Tumor Necrosis Factor-α in THP-1 Cells. Evid Based Complement Alternat Med. 2011;2011:7.

Scheiman JM. The impact of nonsteroidal anti-inflammatory drug induced gastropathy. The Am J Manag Care. 2001;7:S10-S14.

Schwende H, Fitzke E, Ambs P, Dieter P. Differences in the state of differentiation of THP-1 cells induced by phorbol ester and 1,25-dihydroxyvitamin D3. J Leukoc Biol. 1996;59:555−61.

Seo YJ, Jeong M, Lee KT, Jang DS, Choi JH. Isocyperol, isolated from the rhizomes of Cyperus rotundus, inhibits LPS-induced inflammatory responses via suppression of the NF-κB and STAT3 pathways and ROS stress in LPS-stimulated RAW 264.7 cells. Int Immunopharmacol. 2016;38:61–69.

Stuehr DJ, Cho HJ, Rwon NS, Weise MF, Nathan CF. Purification and characterization of the cytokine-induced macrophage nitric oxide synthase: an FAD- and FMN-containing flavoprotein. Proc Natl Acad Sci USA.1991;88:7773-7777

Tahar SM, Touqui L, Chignard M. Innate immunity and inflammation two facets of the same anti-infectious reaction. Clin Exp Immunol. 2009;156:194−198

Tetsuka T, Daphna-Iken D, Miller BW, Guan Z, Baier LD, Morrison AR. Nitric oxide amplifies interleukin 1-induced cyclooxygenase-2 expression in rat mesangial cells. J Clin Invest. 1996;97:2051–2056.

Trost M, English L, Lemieux S, Courcelles M. The phagosomal proteome in interferon gamma activated macrophages. Immunity. 2009;30:143–154.

Tsuchiya S, Yamabe M, Yamaguchi Y, Kobayashi Y, Konno T, Tada K. Establishment and characterization of a human acute monocytic leukemia cell line (THP-1). Int J Cancer. 1980;26:171-176.

Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide?. Lancet. 1991;337:776-778.

Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. N Engl J Med. 1999;340:1888-99.

World Health Organization. WHO Traditional Medicine: Definitions. 2014. Available at: http://www.who.int/medicines/areas/traditional/definitions/en/ (accessed on 01th May 2018).

Wu SJ, Tsai JY, Lai MN, Ng LT. Armillariella mellea Shows Anti-inflammatory Activity by Inhibiting the Expression of NO, iNOS, COX-2 and Cytokines in THP-1 Cells. Am J Chin Med. 2007;35:507-516.