

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 microorganisms 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 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 prophylaxis of chronic diseases is being investigated at the present time (Agarwal and Rao, 2000; Brandi, 1997; Craig, 1999; Lerner, 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 formulated 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 employed in the circular virus vaccine. RAW 264.7 macrophages are capable of antibody dependent 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 not monocytes but dividing macrophages (Lorkowski, 201; Ralph and Nakanishi, 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+} / calmodulin-dependent. iNOS is functionally Ca^{2+} / calmodulin 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 pathogenesis 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 γ (INF- γ) 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	<i>Lilium brownii</i> var. <i>viridulum</i>	Ma et al., 2017
Raw 264.7	<i>Euphorbia supina</i>	Chae et al., 2014
Raw 264.7	<i>Physalis minima</i>	Li et al., 2017
Raw 264.7	<i>Panax ginseng</i>	Jang et al., 2016
Raw 264.7	<i>Cyperus rotundus</i>	Seo et al., 2016
Raw 264.7	<i>Alfalfa</i>	Choi et al., 2013
Raw 264.7	<i>Aurea helianthus</i>	Kim et al., 2017
Raw 264.7	<i>blackberry wine</i>	Caillot et al., 2018
Raw 264.7	<i>Parinari curatellifolia</i>	Gororo et al 2016
Raw 264.7	<i>Humulus japonicus</i>	Lim et al., 2016
Raw 264.7	<i>Taraxacum officinale</i> Weber	Park et al., 2011
Raw 264.7	<i>Citrus reticulata</i>	Jung et al., 2007
Raw 264.7	<i>Annona muricata</i>	Kim et al., 2016
Raw 264.7	<i>Dendropanax morbifera</i> Leveille	Akram et al., 2016
Raw 264.7	<i>Portulaca oleracea</i> L.	Meng et al., 2016
Raw 264.7	<i>Angelica decursiva</i>	Ishita et al., 2016
Raw 264.7	<i>Fragaria vesca</i>	Liberal et al., 2014
THP-1	<i>Hypericum triquetrifolium</i>	Saad et al., 2011
THP-1	<i>Armillariella mellea</i>	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-1 β). (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 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 (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.

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