The Pharmstudent 28 (2017): 18–26

THERAPEUTIC POTENTIAL OF ROSMARINIC ACID IN MYOCARDIAL INFARCTION AND POST-MYOCARDIAL INFARCTION DEPRESSION: THE ROLE OF TUMOR NECROSIS FACTOR-α

Mukesh Kumar and Prasanta Kumar Nayak*

Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, Uttar Pradesh, India.

***Corresponding author: Dr. Prasanta Kumar Nayak,** Assistant Professor, Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, Uttar Pradesh, India.
E-mail: pknayak.phe@iitbhu.ac.in; Telephone: +919099031945.

ABSTRACT

Myocardial infarction patients are more prone to develop depression, which further increases the adverse cardiac outcome. The current pharmacotherapeutic strategy of myocardial infarction improves cardiovascular outcomes without any effects on depression. On the other hand, antidepressant drugs in myocardial infarction patients have shown minimal improvement in depressive symptoms while some of them are worsening the cardiac outcome. A clear understanding of the underlying mechanism of interaction between myocardial infarction and post-myocardial infarction depression remains obscure. However, the pro-inflammatory cytokine particularly, tumor necrosis factor-α has been suggested as a common mechanism of interaction between myocardial infarction and depression. Tumor necrosis factor- α produced during myocardial infarction causes perturbation of blood-brain barrier and interrupts the normal brain functioning leading to depression. Phytochemicals such as rosmarinic acid have shown marked efficacy against various disorders such as heart failure, psoriasis, cancer, and ankylosing spondylitis via inhibition of tumor necrosis factor-α activity. We hypothesize that rosmarinic acid could inhibit the tumor necrosis factor-α in the myocardium as well as inhibit the intrusion of same into the brain through blood brain barrier. We emphasize the therapeutic potential of rosmarinic acid to treat the patients suffering from both conditions of myocardial infarction and post- myocardial infarction depression.

KEY WORDS: Myocardial infarction, post-myocardial infarction depression, rosmarinic acid, tumor necrosis factor-α, phytochemicals.

INTRODUCTION

Myocardial infarction (MI) is the irreversible injury of myocardium due to prolonged ischemia and hypoxia (Thygesen et al., 2012; Kumar et al., 2016). MI is a leading cause of morbidity and mortality in both developed and developing countries (Thygesen et al., 2012). In recent years, clinicians and basic researchers become more interested in understanding the interactive relationship between MI and depression (Smallheer et al., 2017). There is a bidirectional relationship between these

Published by The Pharmaceutical Society, Department of Pharmaceutical Engineering & Technology, IIT (BHU), Varanasi, India

two disorders; MI Patients have a high risk of developing depression while depressive patients have a high risk of experiencing a cardiovascular event (Liu et al., 2013; Reppermund and Tsang, 2016). A recent meta-analysis has reported 1.6- to 2.7-fold increase in the risk of worsening cardiac outcomes in post-MI depressive patients (Meijer et al., 2013). At the moment, a clear understanding of the underlying mechanism of interaction between MI and post-MI depression remains obscure. However, the inflammatory pathway has been suggested as a common pathway of interaction (Liu et al., 2013; Halaris, 2016). Necrosis of myocardium following ischemia triggers an intense inflammatory response, which plays a vital role in the pathogenesis and progression of myocardial infarction (Marchant et al., 2012; Frangogiannis, 2014). In response to myocardial damage, the release of endogenous molecules called 'alarmins' further activates the downstream pro-inflammatory pathways (Frangogiannis, 2008, 2014). The pro-inflammatory cytokines, particularly tumor necrosis factor (TNF)-α, interleukin-1β, and interleukin-6 released by leukocytes, fibroblasts, and endothelial cells have been suggested as key inflammatory mediators involved in the pathophysiology of MI (Frangogiannis et al., 1998; Dewald et al., 2004). The infiltrations of the peripheral immune signal into the brain may interfere with the brain activity while the reverse transfer of immune signal from the brain to the periphery is rare (Liu et al., 2013). Earlier studies have reported that inflammatory mediators produced during MI causes perturbation of blood-brain barrier (BBB) and interrupt the normal brain function (Abbott, 2000; Li and Patel, 2003; Müller and Schwarz, 2007).

An over-activated immune system has been observed in both MI and depressed patients (Bodi et al., 2008; Müller et al., 2011) with significantly high plasma levels of TNF-α in MI patients (Lissoni et al., 1992; Francis et al., 2003). The elevated levels of TNF-α enhance the permeability of BBB via mechanisms such as nitric oxide pathway, cyclooxygenase (COX) pathway, increased leukocyte migration to endothelium and disruption of the endothelial cells architecture (Henry and Duling, 2000; Bove et al., 2001; Liu et al., 2013). In this connection, several in-vitro and in-vivo studies have demonstrated the effects of TNF-α on the BBB permeability (de Vries et al., 1996; Mark and Miller, 1999; Dickstein et al., 2000; Mayhan, 2002). The primarily affected neuroanatomical region in the brain is parts of bulbus olfactorius, somatosensory cortex, parietal and entorhinal cortex, hypothalamus, substantia nigra, cerebellum, spinal trigeminal nucleus, and the periambiguus area (TerHorst et al., 1996; Ter Horst et al., 1997). More specifically, the paraventricular nucleus (PVN) of the hypothalamus has gained much attention in cardiovascular research because it contributes to the sympathetic nervous system activity in both normal and pathological state (Li and Patel, 2003). The peripheral immune activation during MI has been reported to increase the inflammatory cytokine levels and neuronal activity in the PVN (Felder et al., 2003; Guggilam et al., 2007; Leenen, 2007). More recently, it has been reported that activated microglia in the PVN increases the production of cytokines, COX-2, and PGE-2 (Kang et al., 2006; Rana et al., 2010; Yu et al., 2010).

Pharmacological, mechanical, and combined reperfusion techniques form the current treatment strategy for MI, and antidepressants, cognitive behavioral therapy, and physical activity forms the treatment strategy for post-MI depression

Published by The Pharmaceutical Society, Department of Pharmaceutical Engineering & Technology, IIT (BHU), Varanasi, India

(Wang et al., 2011; Ibáñez et al., 2015). The current antidepressant drugs have minimal or no effect on the cardiac outcome while some of them worsening the cardiac outcomes (Akhondzadeh et al., 2003; Marano et al., 2011; Waring, 2012). There is no evidence of treatment strategy that improves cardiac outcome as well as depressive symptoms in MI patients. However, targeting inflammation may improve both cardiac outcomes as well as depressive symptoms in MI patients.

In recent times, natural phytochemicals have gained attention in the field of cardiovascular and neurological research due to their extraordinary mechanisms of action (Shukla et al., 2010; Davinelli et al., 2016). Natural polyphenols such as rosmarinic acid have been demonstrated significant anti-inflammatory activity through several mechanisms includes inhibition of activation of nuclear factor-kappa B (NF-κB), overexpression of pro-inflammatory cytokines, cyclooxygenase-2, and inducible nitric oxide synthase (Veres, 2012; Fazel Nabavi et al., 2015).

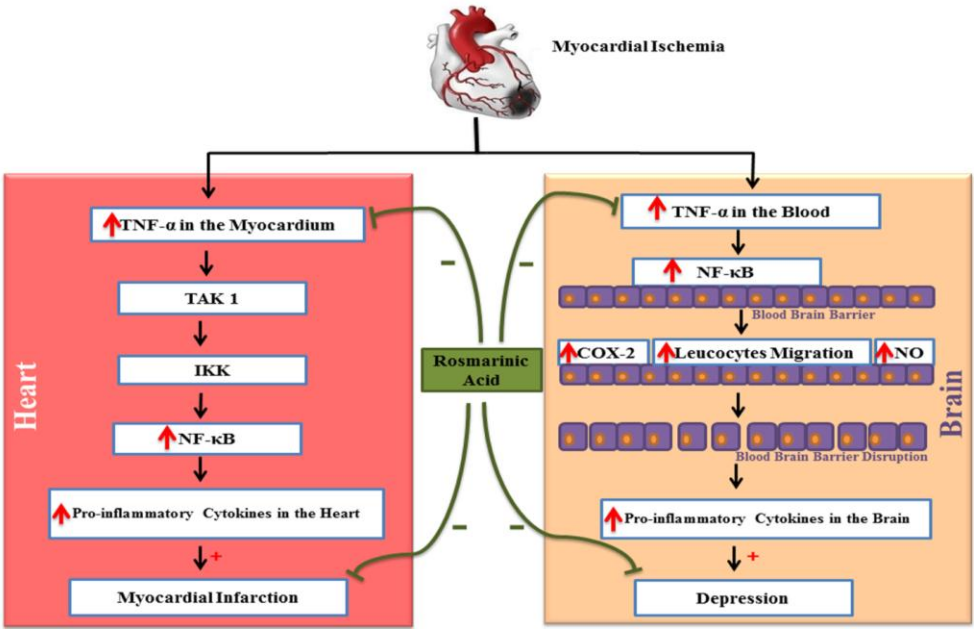

Figure 1: Rosmarinic acid in MI and post-MI depression–a hypothesis. Myocardial ischemia causes an increase in TNF-α production at the ischemic area leading to activation of TAK1 and IKK. The activated IKK further leads to activation of transcription factor NF-κB. NF-κB increases the synthesis of pro-inflammatory cytokines and results in the pathogenesis and progression of MI. On the other hand, the elevated levels of TNF-α in the systemic circulation leads to BBB disruption through NF-κB mediated increase in COX-2, leucocyte migration, and NO release from the endothelial cells of BBB. The disruption of BBB increases the pro-inflammatory cytokines levels in the brain and cause depression. It is hypothesized that rosmarinic acid may inhibit the activity of TNF-α in the heart and the brain to mitigate MI as well as post-MI depression. TAK1, Transforming growth factor-α-activated kinase 1; IKK, I kappa B kinase; TNF-α, Tumor necrosis factor-alpha; COX-2, Cyclooxygenase-2; NO, Nitric oxide; BBB, Blood-brain barrier.

Published by The Pharmaceutical Society, Department of Pharmaceutical Engineering & Technology, IIT (BHU), Varanasi, India

HYPOTHESIS

We hypothesize that rosmarinic acid (RA) could mitigate MI and post-MI depression by inhibiting the TNF-α activity in the myocardium and inhibiting the intrusion of it into the brain. The consideration of TNF-α as a target is supported by findings of various preclinical and clinical studies pertaining to diseases such as heart-failure, psoriasis, ankylosing spondylitis, schizophrenia, bipolar disorder, and breast cancer (Grippo et al., 2003; Tyring et al., 2006; Ertenli et al., 2012; Kappelmann et al., 2016; Hoseth et al., 2017; Ji et al., 2017). The schematic representation of our hypothesis is given in Figure 1.

TNF-α INHIBITORY ACTIVITY OF ROSMARINIC ACID

Rosmarinic acid (α-o-caffeoyl-3,4-dihydroxy phenyl lactic acid) is polyphenolic compound commonly found in Rosmarinus officinalis, Salvia officinalis, and Perilla frutescens. RA has been extensively investigated due to its putative anti-inflammatory activity in cancer research. Although pre-clinical and clinical studies have shown its potential against different types of cancers, the possibility that it could as well be useful for prevention and cure of cardiovascular disorders particularly myocardial infarction remain unanswered (Ferreira et al., 2013; González-Vallinas et al., 2015). Earlier laboratory pharmacokinetic studies demonstrated good bioavailability and pharmacokinetic of RA (Nakazawa and Ohsawa, 1998; Baba et al., 2004; Konishi and Kobayashi, 2005). The clinical study of RA in the management of knee osteoarthritis pain symptoms has shown promising results (Connelly et al., 2014). The optimal pharmacokinetic property combined with its anti-inflammatory activity may facilitate its interaction with multiple protein targets and make RA a multifaceted therapeutic drug candidate. RA has shown TNF-α inhibitory activity in various preclinical studies. Osakabe and colleagues investigated the anti-inflammatory activity of RA in lipopolysaccharide-induced liver injury by measuring the m-RNA level of TNF-α via RT-PCR. RA significantly modulate the mRNA expression of TNF-α (Osakabe et al., 2002). RA has been reported to inhibit TNF-α induced NF-κB activation and reactive oxygen species formation in human dermal fibroblasts (Moon et al., 2010). Kim and colleagues proposed that RA could block TNF-α-dependent NF-κB activation through inhibition of IκBα phosphorylation (Moon et al., 2010). RA has been shown to decrease the mRNA expressions of TNF-α in the nasal mucosa tissue and spleen of ovalbumin-sensitized mice and showed marked anti-inflammatory activity against allergic inflammatory reactions. It was further encouraged to use in allergic rhinitis and allergic rhinoconjunctivitis (Oh et al., 2011).

Rosmarinic acid could offer two major advantages, firstly; it could inhibit the inflammatory phase of MI resulting in reduced activation/accumulation of pro-inflammatory cytokines in the myocardium as well as in the systemic circulation. Due to the strong TNF-α modulating property of RA, it could inhibit the downstream TNF-α signaling pathway that activates the other mediators of inflammation such as NF-κB, IL-1B, and IL-6. Secondly, RA could directly inhibit the TNF-α mediated BBB permeability or inhibit TNF-α activity in the PVN (Song et al., 2016).

Published by The Pharmaceutical Society, Department of Pharmaceutical Engineering & Technology, IIT (BHU), Varanasi, India

CONCLUSION

Rosmarinic acid has a promising potential to inhibit TNF-α activity in the myocardium as well as in the BBB, and it may further prevent intrusion of TNF-α into the brain. This hypothesis could help researchers to explore the potential of RA in the treatment of MI and post-MI depression, which is highly relevant from patients as well as a society perspective.

ACKNOWLEDGEMENT

Mukesh Kumar would like to thank the Indian Institute of Technology (Banaras Hindu University) Varanasi for the teaching assistantship.

CONFLICT OF INTEREST

Authors of the manuscript declare no conflict of interest.

REFERENCES

Abbott NJ (2000) Inflammatory mediators and modulation of blood–brain barrier permeability. Cellular and Molecular Neurobiology 20:131-147.

Akhondzadeh S, Faraji H, Sadeghi M, Afkham K, Fakhrzadeh H, Kamalipour A (2003) Double-blind comparison of fluoxetine and nortriptyline in the treatment of moderate to severe major depression. Journal of Clinical Pharmacy and Therapeutics 28:379-384.

Baba S, Osakabe N, Natsume M, Terao J (2004) Orally administered rosmarinic acid is present as the conjugated and/or methylated forms in plasma, and is degraded and metabolized to conjugated forms of caffeic acid, ferulic acid and m-coumaric acid. Life Sciences 75:165-178.

Bodi V, Sanchis J, Nunez J, Mainar L, Minana G, Benet I, Solano C, Chorro FJ, Llacer A (2008) Uncontrolled immune response in acute myocardial infarction: unraveling the thread. American Heart Journal 156:1065-1073.

Bove K, Neumann P, Gertzberg N, Johnson A (2001) Role of ecNOS-derived NO in mediating TNF-induced endothelial barrier dysfunction. American Journal of Physiology Lung Cellular and Molecular Physiology 280:L914-L922.

Connelly AE, Tucker AJ, Tulk H, Catapang M, Chapman L, Sheikh N, Yurchenko S, Fletcher R, Kott LS, Duncan AM (2014) High-rosmarinic acid spearmint tea in the management of knee osteoarthritis symptoms. Journal of Medicinal Food 17:1361-1367.

Davinelli S, Maes M, Corbi G, Zarrelli A, Willcox DC, Scapagnini G (2016) Dietary phytochemicals and neuro-inflammaging: from mechanistic insights to translational challenges. Immunity & Ageing 13:DOI 10.1186/s12979-12016-10070-12973.

de Vries HE, Blom-Roosemalen MC, van Oosten M, de Boer AG, van Berkel TJ, Breimer DD, Kuiper J (1996) The influence of cytokines on the integrity of the blood-brain barrier in vitro. Journal of Neuroimmunology 64:37-43.

Dewald O, Ren G, Duerr GD, Zoerlein M, Klemm C, Gersch C, Tincey S, Michael LH, Entman ML, Frangogiannis NG (2004) Of mice and dogs: species-specific differences in the inflammatory response following myocardial infarction. The American Journal of Pathology 164:665-677.

Dickstein JB, Moldofsky H, Hay JB (2000) Brain-blood permeability: TNF-α promotes escape of protein tracer from

CSF to blood. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 279:R148-R151.

Ertenli I, Ozer S, Kiraz S, Apras S, Akdogan A, Karadag O, Calguneri M, Kalyoncu U (2012) Infliximab, a TNF-alpha antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. Rheumatology International 32:323-330.

Fazel Nabavi S, Carlo Tenore G, Daglia M, Tundis R, Rosa Loizzo M, Mohammad Nabavi S (2015) The cellular protective effects of rosmarinic acid: from bench to bedside. Current Neurovascular Research 12:98-105.

Felder RB, Francis J, Zhang Z-H, Wei S-G, Weiss RM, Johnson AK (2003) Heart failure and the brain: new perspectives. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 284:R259-R276.

Ferreira LG, Celotto AC, Capellini VK, Albuquerque AAS, Nadai TRd, Carvalho MTMd, Evora PRB (2013) Does rosmarinic acid underestimate as an experimental cardiovascular drug? Acta Cirurgica Brasileira 28:83-87.

Francis J, Weiss RM, Johnson AK, Felder RB (2003) Central mineralocorticoid receptor blockade decreases plasma TNF-α after coronary artery ligation in rats. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 284:R328-R335.

Frangogiannis NG (2008) The immune system and cardiac repair. Pharmacological Research 58:88-111.

Frangogiannis NG (2014) The immune system and the remodeling infarcted heart: cell biological insights and therapeutic opportunities. Journal of Cardiovascular Pharmacology 63:185-195.

Frangogiannis NG, Lindsey ML, Michael LH, Youker KA, Bressler RB, Mendoza LH, Spengler RN, Smith CW, Entman ML (1998) Resident cardiac mast cells degranulate and release preformed TNF-α, initiating the cytokine cascade in experimental canine myocardial ischemia/reperfusion. Circulation 98:699-710.

González-Vallinas M, Reglero G, Ramírez de Molina A (2015) Rosemary (Rosmarinus officinalis L.) extract as a potential complementary agent in anticancer therapy. Nutrition and Cancer 67:1223-1231.

Grippo AJ, Francis J, Weiss RM, Felder RB, Johnson AK (2003) Cytokine mediation of experimental heart failure-induced anhedonia. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 284:R666-R673.

Guggilam A, Haque M, Kerut EK, McIlwain E, Lucchesi P, Seghal I, Francis J (2007) TNF-α blockade decreases oxidative stress in the paraventricular nucleus and attenuates sympathoexcitation in heart failure rats. American Journal of Physiology-Heart and Circulatory Physiology 293:H599-H609.

Halaris A (2016) Inflammation-Associated Co-morbidity Between Depression and Cardiovascular Disease. In: Inflammation-Associated Depression: Evidence, Mechanisms and Implications, vol. 31 (Dantzer, R. and Capuron, L., eds), pp 45-70 Cham Springer.

Henry CB, Duling BR (2000) TNF-α increases entry of macromolecules into luminal endothelial cell glycocalyx. American Journal of Physiology-Heart and Circulatory Physiology 279:H2815-H2823.

Published by The Pharmaceutical Society, Department of Pharmaceutical Engineering & Technology, IIT (BHU), Varanasi, India

Hoseth EZ, Ueland T, Dieset I, Birnbaum R, Shin JH, Kleinman JE, Hyde TM, Mørch RH, Hope S, Lekva T (2017) A study of TNF pathway activation in schizophrenia and bipolar disorder in plasma and brain tissue. Schizophrenia Bulletin 43:881-890.

Ibáñez B, Heusch G, Ovize M, Van de Werf F (2015) Evolving therapies for myocardial ischemia/reperfusion injury. Journal of the American College of Cardiology 65:1454-1471.

Ji X, Peng Z, Li X, Yan Z, Yang Y, Qiao Z, Liu Y (2017) Neutralization of TNFα in tumor with a novel nanobody potentiates paclitaxel-therapy and inhibits metastasis in breast cancer. Cancer Letters 386:24-34.

Kang Y-M, Zhang Z-H, Johnson RF, Yu Y, Beltz T, Johnson AK, Weiss RM, Felder RB (2006) Novel effect of mineralocorticoid receptor antagonism to reduce proinflammatory cytokines and hypothalamic activation in rats with ischemia-induced heart failure. Circulation Research 99:758-766.

Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM (2016) Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Molecular Psychiatry doi:10.1038/mp.2016.1167.

Konishi Y, Kobayashi S (2005) Transepithelial transport of rosmarinic acid in intestinal Caco-2 cell monolayers. Bioscience, Biotechnology, and Biochemistry 69:583-591.

Kumar M, Kasala ER, Bodduluru LN, Dahiya V, Sharma D, Kumar V, Lahkar M (2016) Animal models of myocardial infarction: mainstay in clinical translation. Regulatory Toxicology and Pharmacology 76:221-230.

Leenen FH (2007) Brain mechanisms contributing to sympathetic hyperactivity and heart failure. Circulation Research 101:221-223.

Li YF, Patel KP (2003) Paraventricular nucleus of the hypothalamus and elevated sympathetic activity in heart failure: the altered inhibitory mechanisms. Acta Physiologica Scandinavica 177:17-26.

Lissoni P, Pelizzoni F, Mauri O, Perego M, Pittalis S, Barni S (1992) Enhanced secretion of tumour necrosis factor in patients with myocardial infarction. The European Journal of Medicine 1:277-280.

Liu H, Luiten PG, Eisel UL, Dejongste MJ, Schoemaker RG (2013) Depression after myocardial infarction: TNF-α-induced alterations of the blood–brain barrier and its putative therapeutic implications. Neuroscience & Biobehavioral Reviews 37:561-572.

Marano G, Traversi G, Romagnoli E, Catalano V, Lotrionte M, Abbate A, Biondi-Zoccai G, Mazza M (2011) Cardiologic side effects of psychotropic drugs. Journal of Geriatric Cardiology 8:243-253.

Marchant DJ, Boyd JH, Lin DC, Granville DJ, Garmaroudi FS, McManus BM (2012) Inflammation in myocardial diseases. Circulation Research 110:126-144.

Mark KS, Miller DW (1999) Increased permeability of primary cultured brain microvessel endothelial cell monolayers following TNF-α exposure. Life Sciences 64:1941-1953.

Mayhan WG (2002) Cellular mechanisms by which tumor necrosis factor-α produces disruption of the blood–brain barrier. Brain Research 927:144-152.

Meijer A, Conradi H, Bos E, Anselmino M, Carney R, Denollet J, Doyle F,

Published by The Pharmaceutical Society, Department of Pharmaceutical Engineering & Technology, IIT (BHU), Varanasi, India

Freedland K, Grace S, Hosseini S (2013) Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis. The British Journal of Psychiatry 203:90-102.

Moon D-O, Kim M-O, Lee J-D, Choi YH, Kim G-Y (2010) Rosmarinic acid sensitizes cell death through suppression of TNF-α-induced NF-κB activation and ROS generation in human leukemia U937 cells. Cancer Letters 288:183-191.

Müller N, Myint A-M, Schwarz MJ (2011) Inflammatory biomarkers and depression. Neurotoxicity Research 19:308-318.

Müller N, Schwarz M (2007) The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. Molecular Psychiatry 12:988-1000.

Nakazawa T, Ohsawa K (1998) Metabolism of rosmarinic acid in rats. Journal of Natural Products 61:993-996.

Oh H-A, Park C-S, Ahn H-J, Park YS, Kim H-M (2011) Effect of Perilla frutescens var. acuta Kudo and rosmarinic acid on allergic inflammatory reactions. Experimental Biology and Medicine 236:99-106.

Osakabe N, Yasuda A, Natsume M, Sanbongi C, Kato Y, Osawa T, Yoshikawa T (2002) Rosmarinic acid, a major polyphenolic component of Perilla frutescens, reduces lipopolysaccharide (LPS)-induced liver injury in D-galactosamine (D-GalN)-sensitized mice. Free Radical Biology and Medicine 33:798-806.

Rana I, Stebbing M, Kompa A, Kelly DJ, Krum H, Badoer E (2010) Microglia activation in the hypothalamic PVN following myocardial infarction. Brain Research 1326:96-104.

Reppermund S, Tsang RS (2016) The Risk Relationship Between Depression and CVD During Ageing. In: Cardiovascular Diseases and Depression(Baune, B. and Tully, P., eds), pp 23-36 Cham: Springer.

Shukla SK, Gupta S, Ojha SK, Sharma SB (2010) Cardiovascular friendly natural products: a promising approach in the management of CVD. Natural Product Research 24:873-898.

Smallheer BA, Vollman M, Dietrich MS (2017) Learned Helplessness and Depressive Symptoms Following Myocardial Infarction. Clinical Nursing Research https://doi.org/10.1177/1054773816689752.

Song H, Xu L, Zhang R, Cao Z, Zhang H, Yang L, Guo Z, Qu Y, Yu J (2016) Rosemary extract improves cognitive deficits in a rats model of repetitive mild traumatic brain injury associated with reduction of astrocytosis and neuronal degeneration in hippocampus. Neuroscience Letters 622:95-101.

Ter Horst GJ, Nagel JG, De Jongste MJ, Van der Werf YD (1997) Selective blood brain barrier dysfunction after intravenous injections of rTNFα in the rat. In: Neurochemistry, pp 141-146: Springer.

TerHorst G, VanderWerf Y, DeJongste M (1996) Acute myocardial infarction and cytokine-mediated selective blood brain barrier leakage in the rat. In: Journal of Neurochemistry, vol. 66, pp S54-S54: Lippincott-Raven, Philadelphia.

Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD (2012) Third universal definition of myocardial infarction. Circulation 126:2020-2035.

Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R (2006) Etanercept

Published by The Pharmaceutical Society, Department of Pharmaceutical Engineering & Technology, IIT (BHU), Varanasi, India

and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. The Lancet 367:29-35.

Veres B (2012) Anti-inflammatory role of natural polyphenols and their degradation products. In: Severe Sepsis and Septic Shock—Understanding a Serious Killer(Fernandez, R., ed), pp 379-410 Croatia: InTech.

Wang JT, Hoffman B, Blumenthal JA (2011) Management of depression in patients with coronary heart disease: association, mechanisms, and treatment implications for depressed cardiac patients. Expert Opinion on Pharmacotherapy 12:85-98.

Waring WS (2012) Clinical use of antidepressant therapy and associated cardiovascular risk. Drug Healthc Patient Saf 4:93-101.

Yu Y, Zhang Z-H, Wei S-G, Serrats J, Weiss RM, Felder RB (2010) Brain perivascular macrophages and the sympathetic response to inflammation in rats after myocardial infarction. Hypertension 55:652-659.

~§~

Published by The Pharmaceutical Society, Department of Pharmaceutical Engineering & Technology, IIT (BHU), Varanasi, India