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Efeito da amitriptilina em um modelo murino de colite

São Paulo
2015

RESUMO

NAMAZU, L. B. **Efeito da amitriptilina em um modelo murino de colite.** [Effect of amitriptyline in a murine model of colitis]. 2015. 162f. Tese (Doutorado em Ciências) - Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo, 2015.

Doenças inflamatórias intestinais (DII) em humanos são reações crônicas de etiologia complexa. Trata-se de uma reação imunológica exacerbada e depende da microbiota. O sistema nervoso interage com a imunidade do intestino de um modo bidirecional. Relatos clínicos e poucos achados experimentais apontam para uma ligação entre transtornos depressivos e doenças inflamatórias intestinais, sugerindo interação neuroimunológica na patogenia deste processo. Ainda, o tratamento de Doenças inflamatórias intestinais (DII- Doença de Crohn e Colite Ulcerativa) com antidepressivos em modelos murino de colite têm sugerido bons resultados na redução da inflamação. O mecanismo da inflamação na DII e a participação do sistema nervoso ou da modulação de tal processo pelo emprego de antidepressivos ainda não está totalmente elucidado. Este estudo teve como objetivo estudar o efeito do antidepressivo amitriptilina em um modelo murino de colite. A colite foi induzida em camundongos C57BL/6 por Dextrano Sulfato de Sódio (DSS) e a amitriptilina (AMT) foi administrada por via oral, em regime profilático ou terapêutico. Avaliamos a dose de AMT no teste de suspensão da cauda (TSC), o acúmulo de neutrófilos pela atividade de mieloperoxidase (MPO), burst oxidativo, curva de sobrevida, histopatologia do intestino, atividade da doença por sintomas clínicos, a depleção de muco intestinal, citocinas inflamatórias no cólon e no soro, fenotipagem de linfócitos T $CD4^+$, T $CD8^+$ e monócitos $CD14^+$. Resultados: A dose de AMT (200 µg/ml) e os regimes de tratamento utilizados aqui foram capazes de impedir ou diminuir a histopatologia da colite, os sinais clínicos (ganho de peso (%), comprimento e peso do cólon) e a mortalidade dos animais no modelo terapêutico do grupo inflamado e tratado com AMT. A atividade de MPO, níveis circulantes de IL- 1β, IL- 6 e TNF- α foram reduzidas nos dois protocolos experimentais (profilático e terapêutico). Conclusões: Este estudo incluiu um período de tratamento prolongado, visto que os antidepressivos são conhecidos por serem eficazes em seres humanos depois de várias semanas a meses de prescrição, e confirmou a eficiência da via de administração oral, uma vez que os antidepressivos são geralmente administrados por via oral a seres humanos. Este

regime de tratamento melhorou o potencial anti-inflamatório de AMT na redução DSS-colite em camundongos, com base nos parâmetros estudados.

Palavras-chave: Doença inflamatória intestina. Amitriptilina. Neuroimunomodulação.

ABSTRACT

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Inflammatory bowel disease (IBD) in humans is a complex etiology of chronic reactions. It is an exacerbated immune reaction and depends on the microflora. The nervous system interacts with the intestinal immunity of a bidirectional fashion. Clinical reports and few experimental findings point to a link between depressive disorders and inflammatory bowel disease, suggesting neuroimmunological interaction in the pathogenesis of this process. Also, treatment of inflammatory bowel diseases (Crohn's disease DII- and Ulcerative Colitis) with antidepressants in murine models of colitis have pointed to positive results in reducing inflammation. The mechanism of inflammation in IBD and the involvement of the nervous system or modulation of this process by the use of antidepressants is not yet fully elucidated. This study aimed to study the effect of amitriptyline in a murine model of colitis. Colitis was induced in C57BL / 6 mice by Dextran Sodium Sulfate (DSS) and amitriptyline (AMT) were orally administered in a prophylactic or therapeutic regimen. We evaluated the AMT dose in the tail suspension test (TST), the accumulation of neutrophils by myeloperoxidase activity (MPO), oxidative burst, survival curve, bowel histopathology, disease activity by clinical symptoms, depletion of intestinal mucus, colon and inflammatory cytokines in the serum phenotype of $CD4^+$ T lymphocytes, $CD8^+$ and $CD14^+$ monocytes. Results: The dose of AMT (200 µg / ml) and treatment regimens used herein are able to prevent or decrease the pathology of colitis, clinical signs (weight gain (%), colon weight and length) and mortality animals in the therapeutic model inflamed group and treated with AMT. MPO activity, circulating levels of IL-1β, IL-6 and TNF-α were reduced in both experimental protocols (prophylactic and therapeutic). Conclusions: This study included a prolonged period of treatment, as antidepressants are known to be effective in humans after several weeks or months of limitation, and confirmed the effectiveness of oral administration route, since antidepressants are generally administered orally to humans. This treatment scheme has improved potential anti-inflammatory AMT in reducing DSS colitis in mice based on the study parameters.

Keywords: Inflammatory bowel disease, Amitriptyline, Neuroimmunomodulation.

1 INTRODUÇÃO

As Doenças inflamatórias do intestino (DII) compreendem duas classes: Retocolite ulcerativa ou Colite Ulcerativa (CU) e Doença de Crohn (DC). DII é uma doença inflamatória crônica recorrente, de etiologia sob investigação, mas envolve uma reação imune inadvertida para o intestino, desencadeada por fatores intrínsecos (SATSANGI et al., 1998; XAVIER; PODOLSKY, 2007; KASER; ZEISSIG; BLUMBERG, 2010) e fatores ambientais que incluem a microbiota (RAMPTON, 2000; PODOLSKY, 2002; NG et al., 2013). A prevalência de DII permanece em ascensão nos EUA, norte da Europa e começa a aumentar nos países do Oriente e do hemisfério sul e a maior parte do mundo em desenvolvimento (DE SCHEPPER et al., 2008; PERSE; CERAR, 2012). Registros emergentes da DII estão associados com o aumento de hábitos culturais das sociedades ocidentais em países como a China, Coreia do Sul, Índia, Líbano, Irã, Tailândia e norte da África, embora dados precisos destas áreas não estivessem disponíveis (NG et al., 2013).

Os modelos murino de colite intensificaram a identificação das funções do sistema imunitário da mucosa que cooperam para manter a homeostase intestinal, que incluem a presença de uma barreira epitelial intacta, o desenvolvimento de respostas imunes inatas eficientes, a manutenção de um equilíbrio delicado entre respostas das células T efetoras e reguladoras, bem como o estabelecimento de inflamação fisiológica (VALATAS; VAKAS; KOLIOS, 2003; STURM; DE SOUZA; FIOCCHI, 2008). Apesar da variedade de modelos animais que imitam diferentes aspectos de DII humana, a probabilidade de tradução de estudos com animais de intervenção em uso clínico continua a ser bastante limitado (VALATAS; VAKAS; KOLIOS, 2003).

A colite induzida em camundongos por Dextrano Sulfato de Sódio (DSS-colite) é um modelo experimental simples (PERSE; CERAR, 2012) que pode ser utilizado por reproduzir DII aguda, crônica recorrente dependente da frequência e número de ciclos de tratamento por DSS (OKAYASU et al., 1990). Várias características histopatológicas da DII, incluindo algumas de etiologia ainda desconhecida, como a displasia em CU, ocorre espontaneamente na fase crônica da colite- DSS (COOPER et al., 1993). Danos epiteliais do cólon (DIELEMAN et al., 1994) disbiose da microbiota luminal (YAMADA; OHKUSA;

OKAYASU, 1992) e ativação de macrófagos residentes e infiltrados (OHKUSA et al., 1995) são alguns mecanismos propostos subjacentes ao dano tecidual por colite- DSS que pode recapitular a doença que ocorre naturalmente (MAHLER et al., 1998). Dados de estudos por DSS empregam drogas potencialmente terapêuticas que demostram que a colite-DSS pode ser reproduzida com sucesso por apresentar características discretas da doença humana, ajudando na conversão de dados de camundongos para doenças humanas (MELGAR et al., 2008).

Os estudos clínicos e experimentais indicam uma exacerbação da inflamação intestinal, por condições emocionais e psiquiátricas, como a depressão (GHIA; BLENNERHASSETT; COLLINS, 2008), o que pode contribuir para o desenvolvimento e recorrência da DII (GRAFF; WALKER; BERNSTEIN, 2009). Outros estudos afirmam que a depressão é um epifenômeno marginalmente associado à depressão e seu papel na recorrência é controverso (VARGHESE et al., 2006; GHIA; BLENNERHASSETT; COLLINS, 2008). Enquanto alguns estudos apontam para uma alta influência da depressão sobre o índice de atividade da doença (HELZER et al., 1984; KURINA et al., 2001; GRAFF; WALKER; BERNSTEIN, 2009), outros relatos apontam como sendo secundária a atividade da doença (KURINA et al., 2001; MARDINI; KIP; WILSON, 2004).

Na direção oposta, mas complementar, várias hipóteses implicam o sistema imunológico sobre a etiologia da depressão. Teorias como a imuno-inflamação, citocinérgica e macrofágica como um fenômeno psiconeuroimune (SMITH, 1991). A base para esta hipótese é consistente com um aumento da concentração de citocinas pró-inflamatórias (LICINIO; WONG, 1999) que frequentemente levam a depressão, como alterações do comportamento (ANISMAN; MERALI, 2003; CAPURON; DANTZER, 2003). Portanto, a literatura aponta uma interferência entre a inflamação e as respostas imunes à emoção e depressão por meio de citocinas inflamatórias, tais como IL-1, IL-6 e fator de necrose tumoral alfa (TNF-α) (ANISMAN; MERALI, 2003; CAPURON; DANTZER, 2003; DOWLATI et al., 2010). Na colite ulcerativa, o aumento da secreção de citocinas inflamatórias é considerado chave na progressão desta doença (SAILOR, 1997). A secreção de citocinas é ativamente modulada pelo sistema nervoso autônomo (SNA) (MATSUNAGA et al., 2001).

Os antidepressivos em pacientes com DII visam ajudá-los a lidar com os seus problemas emocionais e melhorar sua qualidade de vida, além de que a terapia antidepressiva pode influenciar o curso da DII. Os relatórios mostraram que estas drogas equilibraram a desregulação de respostas imunitárias em DII, levando a um prognóstico mais positivo da doença (MIKOCKA-WALUS et al., 2012). A amitriptilina (AMT) é um

antidepressivo tricíclico amplamente utilizado como terapia de apoio para os pacientes que sofrem de DII ou de outros distúrbios gastrointestinais (QUARTERO et al., 2005; AVILA; BOTTINO, 2006). Prescrever amitriptilina, nesses casos, é, supostamente, devido a sua eficácia nos tratamentos psicológicos (SUSSMAN; STAHL, 1996; RAJAGOPALAN; KURIAN; JOHN, 1998; GERSON; TRIADAFILOPOULOS, 2006) e sintomas somáticos associados à DII (MIKOCKA-WALUS et al., 2006).

Neuroimunomodulação é o estudo sobre interações bidirecionais entre os sistemas neuroendócrino e imunológico (COSTA-PINTO; PALERMO-NETO, 2010). A evidência clínica e de dados experimentais suportam que a depressão está associada à inflamação e antidepressivos são eficazes na modulação não só os aspectos emocionais de DII, mas também na própria inflamação. Vários modelos apontam para a relevância das interações neuroimunoendócrinas na doença. Neste estudo focamos em interações neuroimunes no intestino sobre o curso de uma doença inflamatória crônica possibilitando novas possibilidades para combinar a terapia focada no dano tecidual e bem-estar.

CONCLUSÃO

O tratamento com amitriptilina é capaz de atenuar diversos parâmetros analisados em um modelo murinho de colite por DSS. A via de administração oral e o regime de tratamento longo se mostraram eficientes em reduzir a gravidade da colite em camundongos. Enquanto mais estudos são necessários para elucidar os mecanismos para a atenuação da doença observada aqui, podemos concluir que antidepressivos como a amitriptilina, além de prescritos com o intuito de melhorar aspectos psicológicos e emocionais associados a colite em humanos, podem de fato melhorar o curso da doença, tornando-os medicamentos com potencial terapêutico relevante na doença humana.

REFERÊNCIAS

ABBADIE, C. Chemokines, chemokine receptors and pain. **Trends in Immunology**, v. 26, p. 529- 534, 2005.

ABDEL-SALAM, O. M.; NOFAL, S. M.; EL-SHENAWY, S. M. Evaluation of the anti-inflammatory and anti-nociceptive effects of different antidepressants in the rat. **Pharmacological Research**, v. 48, n. 2, p. 157-165, 2003.

ABRAHAM, C.; CHO, J. H. Inflammatory bowel disease. **New England Journal of Medicine**, v. 361, n. 21, p. 2066- 2078, 2009.

ACHAR, E.; ACHAR, R. A.; PAIVA, T. B.; Campos, A. H.; Schor, N. Amitriptyline Eliminates Calculi through Urinary Tract. **Kidney International**, v. 64, n. 4, p. 1356- 1364, 2003.

ADER, R.; COHEN, N. Conditioning of the immune response. **Netherland Journal of Medicine**, v. 39, n. 3-4, p. 263- 273, 1991.

ADER, R. On the development of psychoneuroimmunology. **European Journal Pharmacology**, v. 405, n. 1-3, p. 167- 176, 2000.

ADDOLORATO, G.; CAPRISTO, E.; STEFANINI, G. F.; GASBARRINI, G. Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. **Scandinavian Journal of Gastroenterology**, v. 32, n. 10, p. 1013-1021, 1997.

ALEX, P.; ZACHOS, N. C.; NGUYEN, T.; GONZALES, L. Distinct cytokine patterns identified from multiplex profiles of murine DSS and TNBS-induced colitis. **Inflammatory Bowel Disease**, v. 15, n. 3, p. 341- 352, 2009.

ALLISON, M. C.; POULTER, L. W. Changes in phenotypically distinct mucosal macrophage populations may be a prerequisite for the development of inflammatory bowel disease. **Clinical & Experimental Immunology**, v. 85, p. 504- 509, 1991.

ALPI, A.; COCCHI, A.; MENEGHELLI, A.; PAFUMI, N.; PATELLI, G. Working with families in the early stages of psychosis: a structured intervention for caregivers. **Giornale Italiano di Medicina del Lavoro ed Ergonomia**, v. 30, n. 3, p. B62-70, 2008. Suplement, l B.

ALVES, G. J.; VISMARI, L.; FLORIO, J. C.; PALERMO-NETO, J. Cohabitation with a sick cage mate: Effects on noradrenaline turnover and neutrophil activity. **Neuroscience Research**, v. 56, n. 2, p. 172-179, 2006.

ALVES, G. J.; PALERMO-NETO, J. Neuroimmunomodulation: the cross-talk between nervous and immune systems. **Revista Brasileira Psiquiatria**, v. 29, n. 4, p. 363-369, 2007.

ALVES, G. J.; VISMARI, L.; PALERMO-NETO, J. Cohabitation with a sick cage mate: effects on ascitic form of Ehrlich tumor growth and macrophage activity. **Neuroimmunomodulation**, v. 14, n. 6, p. 297-303, 2007.

ANISMAN, H.; RAVINDRAN, A. V.; GRIFFITHS, J. MERALI, Z. Interleukin-1 beta production in dysthymia before and after pharmacotherapy. **Biology Psychiatry**, v. 46, p. 1649-1655, 1999.

ANISMAN, H.; MERALI, Z. Cytokines, stress and depressive illness: brain-immune interactions. **Annals of Medicine**, v. 35, n. 1, p. 2-11, 2003.

ASTRY, B.; HARBERTS, E.; MOUDGIL, K.D. A cytokine-centric view of the pathogenesis and treatment of autoimmune arthritis. **Journal of Interferon & Cytokine**, v. 31, p. 927-940, 2011.

ATREYA, R.; MUDTER, J.; FINOTTO, S.; MÜLLBERG, J.; JOSTOCK, T.; WIRTZ, S.; SCHÜTZ, M.; BARTSCH, B.; HOLTMANN, M.; BECKER, C.; STRAND, D.; CZAJA, J.; SCHLAAK, J. F.; LEHR, H. A.; AUTSCHBACH, F.; SCHÜRMANN, G.; NISHIMOTO, N.; YOSHIZAKI, K.; ITO, H.; KISHIMOTO, T.; GALLE, P. R.; ROSE-JOHN, S.; NEURATH, M. F. Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in Crohn disease and experimental colitis in vivo. **Nature Medicine**, v. 6, p. 583- 588, 2000.

AVILA, R.; BOTTINO, C. Cognitive changes update among elderly with depressive syndrome. **Revista Brasileira de Psiquiatria**, v. 28, n. 4, p. 316-20, 2006.

AXELSSON, L. G.; LUNDBERG, C.; LANDSTRÖM, E.; BYLUND-FELLENIUS, A. C. The degree of sulfate content and the molecular weight of dextran sulfate and carrageenan are important for the induction of colitis in mice. **Gastroenterology**, v. 110, p. A858, 1996a. Supplement, 4.

AXELSSON, L. E.; LANDSTROM, T.; GOLDSCHMIDT, A.; GRONBERG, A.; BYLUND-FELLENIUS, A. C. Dextran sulfate sodium (DSS) induced experimental colitis in immunodeficient mice: effects in CD4(+) -cell depleted, athymic and NK-cell depleted SCID mice. **Inflammation Research**, v. 45, p. 181- 191, 1996b.

AZUMA, Y. T.; HAGI, K.; SHINTANI, N.; KUWAMURA, M.; NAKAJIMA, H.; HASHIMOTO, H.; BABA, A.; TAKEUCHI, T. Pacap provides colonic protection against dextran sodium sulfate induced colitis. **Journal Cell Physiology**, v. 216, p. 111-119, 2008.

BAI, F.; LI, X.; CLAY, M.; LINDSTROM, T.; SKOLNICK, P. Intra- and interstrain differences in models of ‘behavioral despair’. **Pharmacology Biochemical Behavior**, v. 70, p. 187-192, 2001.

BAILEY, R. W.; BOURNE, E. J. Intracellular glycosidases of dextran-producing bacteria. **Nature**, v. 15, n. 191, p. 277-8, 1961.

BALDESSARINI, R. J. Drug therapy of depression and anxiety disorders. In: BRUNTON, L. L.; LAZO, J. S.; PARKER, K. L. (Ed.). **Goodman and Gilmans the pharmacological basis of therapeutics**. New York: McGraw- Hill., 2006. p. 429-459.

BAMIAS, G.; KALTSA, G.; LADAS, S. D. Cytokines in the pathogenesis of ulcerative colitis. **Discovery Medicine**, v. 11, p. 459- 467, 2011.

BAMIAS, G.; MARTIN, C.; MISHINA, M.; ROSS, W. G.; RIVERA-NIEVES, J.; MARINI, M.; COMINELLI, F. Proinflammatory effects of TH2 cytokines in a murine model of chronic small intestinal inflammation. **Gastroenterology**, v. 128, p. 654- 666, 2005.

BASSO, A. S.; PINTO, F. A.; RUSSO, M.; BRITTO, L. R.; DE SA-ROCHA, L. C.; PALERMO-NETO, Jornal neural correlates of IgE-mediated food allergy. **Journal Neuroimmunology**, v. 140, n. 1-2, p. 69-77, 2003.

BENBERNOU, N.; ESNAULT, S.; SHIN, H. C. K.; FEKKAR, H.; GUENOUNOU, M. Differential regulation of IFN–g, IL–10 and inducible nitric oxide synthase in human T cells by cyclic AMP-dependent signal transduction pathway. **Immunology**, v. 91, p. 361-368, 1997.

BERTOLUCCI, M.; PEREGO, C.; DE SIMONI, M. G. Interleukin-6 is differently modulated by central opioid receptor subtypes. **American Journal of Physiology** , v. 273, p. R956-R959, 1997.

BERTRAND, P. P.; BARAJAS-ESPINOSA, A.; NESHAT, S.; BERTRAND, R. L.; LOMAX, A. E. Analysis of real-timeserotonin (5-HT) availability during experimental colitis in mouse. **American Journal of Physiology - Gastrointestinal and Liver Physiolog**, v. 298, p. G446-G455, 2010.

BESEDOVSKY, H. O.; DEL REY, A. Immune-neuro-endocrine interactions: facts and hypotheses. **Endocrinology Reviews**, v. 17, n. 1, p. 64-102, 1996

BEST, W. R.; BECKTEL, J. M.; SINGLETON, J. W.; KERN, JR. F. Development of a Crohn's disease activity index. National Cooperative Crohn's disease study. **Gastroenterology**, v. 70, p. 439–444, 1976.

BIANCHI, M.; ROSSONI, G.; SACERDOTE, P.; PANERAI, A. E.; BERTI, F. Effects of chlomipramine and fluoxetine on subcutaneous carrageenin-induced inflammation in the rat. **Inflammation Research**, v. 44, p. 466-469, 1995.

BIRGEL, E. H. Hematologia clínica veterinária. In: BIRGEL, E. H.; LARSSON, M.H.M.A.; HAGIWARA, M. K.; VASCONCELOS, S. A.; LARSSON, C. E.; BENESI, F. J. **Patologia clínica veterinária**. São Paulo: Sociedade Paulista de Medicina Veterinária, 1982. p. 2- 49.

BITTENCOURT, S. C.; CAPONI, S; MALUF, S. Medicamentos antidepressivos: inserção na prática biomédica (1941 a 2006) a partir da divulgação em um livro-texto de farmacologia. **Mana,** v. 19, n. 2, p. 219-247, 2013.

BLALOCK, J. E. The immune system as a sensory organ. **Journal Immunology**, v. 132, n. 3, p. 1067-70, 1984.
BLALOCK, J. E. A molecular basis for bidirectional communication between the immune and neuroendocrine systems. **Physiological Reviews**, v. 69, p. 1- 27, 1989.

BLANCHARD, B. A.; GLICK, S. D. Sex differences in mesolimbic dopamine responses to ethanol and relationship to ethanol intake in rats. **Recent Developments in Alcoholism**, v. 12, p. 231- 241, 1995.

BLUTHE, R. M.; MICHAUD, B.; POLI, V.; DANTZER, R. Role of IL-6 in cytokine induced sickness behavior: a study with IL-6 deficient mice. **Physiology and Behavior**, v. 70, n. 3-4, p. 367-373, 2000.

BOISMENU, R.; CHEN, Y. Insights from mouse models of colitis. **Journal of Leukocyte Biology**, v. 67, p. 267- 278, 2000.

BORSINI, F.; MELI, A. Is the forced swimming test a suitable model for revealing antidepressant activity? **Psychopharmacology (Berlim),** v. 94, p. 147- 160, 1988.

BRADLEY, P. P.; PRIEBAT, D. A.; CHRISTENSEN, R. D.; ROTHSTEIN, G. Measurement of cutaneous inflammation: estimation of neutrophil content with an enzyme marker. **Journal of Investigative Dermatology**, v. 78, n. 3, p. 206- 209, 1982.

BRAEGGER, C. P.; NICHOLLS, S.; MURCH, S. H.; STEPHENS, S.; MACDONAL, T. T. Tumour necrosis factor alpha in stool as a marker of intestinal inflammation. **Lancet**, v. 339, p. 89-91, 1992.

BRASIL. MINISTÉRIO DA SAÚDE. **Doenças inflamatórias intestinais surgem da interação de quatro fatores fundamentais; entenda**. Disponível em: <http://sites.uai.com.br/app/noticia/saudeplena/noticias/2014/05/19/noticia_saudeplena,148675/doencas-inflamatorias-intestinais-surgem-da-interacao-de-quatro-fatore.shtml>. Acesso em: 21 Jan. 2015.

BREIDER, M. A.; EPPINGER, M.; GOUGH, A. Intercellular adhesion molecule-1 expression in dextran sodium sulfate-induced colitis in rats. **Veterinary Pathology**, v. 34, p. 598- 604, 1997.

BROWN M. O. Inflammatory bowel disease. **Primary Care**, v. 26, p. 141- 170, 1999.

BRUNTON, L.; PARKER, K.; BLUMENTHAL, D.; BUXTON, I. **Goodman & Gilman's manual of pharmacology and therapeutics**. New York: McGraw Hill, 2008.

BRUSTOLIM, D.; RIBEIRO-DOS-SANTOS, R.; KAST, R. E.; ALTSCHULER, E. L.; SOARES, M. B. A new chapter opens in anti-inflammatory treatments: the antidepressant bupropion lowers production of tumor necrosis factor- alpha and interferon-gamma in mice. **International Immunopharmacology**, v. 6, p. 903-907, 2006.

BYLUND-FELLENIUS, A.C.; LANDSTROMI, E.; AXELSSONT, L. G.; MIDTVEDT, T. Experimental colitis induced by dextran sulphate. M**icrobial ecology in health and disease**, v. 7, p. 207-215, 1994.

CALDARONE, B. J.; KARTHIGEYAN, K.; HARRIST, A.; HUNSBERGER, J. G.; WITTMACK, E.; KING, S. L.; JATLOW, P.; PICCIOTTO, M. R. Sex differences in respone to oral amitriptyline in three animal models of depression in C57BL/6J mice. **Psychopharmacology (Berlim),** v. 170, p. 94-101, 2003.

CALEFI, A. S.; HONDA, B.T.; COSTOLA-DE-SOUZA, C.; DE SIQUEIRA, A.; NAMAZU, L. B.; QUINTEIRO-FILHO, W. M.; FONSECA, J. G.; ALOIA, T. P.; PIANTINO-FERREIRA, A. J.; PALERMO-NETO, J. Effects of long-term heat stress in an experimental model of avian necrotic enteritis. **Poultry Science**, v. 93, n. 6, p. 1344- 1353, 2014.

CAPURON, L.; DANTZER, R. Cytokines and depression: the need for a new paradigm. **Brain, Behavior, and Immunity**, v. 17, n. 1, p. 119-124, 2003.

CARLSSON, A.; FUXE, K.; UNGERSTEDT, U. The effect of imipramine on central 5-hydroxytryptamine neurons. **Journal of Pharmacy and Pharmacology**, v. 20, p. 150- 151, 1968.

CARR, D. J. Neuroendocrine peptide receptors on cells of the immune system. C**hemistry Immunolology**, v. 52, p. 84-105, 1992.

CARTER, M. J.; LOBO, A. J.; TRAVIS, S. P. Guidelines for the management of inflammatory bowel disease in adults. **Gut,** v. 53, n. 5, p. V1- V16, 2004.

CASPER, R. C.; KATZ, M. M.; BOWDEN, C. L.; DAVIS, J. M.; KOSLOW, S. H.; HANIN, I. The pattern of physical symptom changes in major depressive disorder following treatment with amitriptyline or imipramine. **Journal of Affective Disorders**, v. 31, p. 151-64. 1994.

CASTANON, N.; BLUTHÉ, R. M.; DANTZER, R. Chronic treatment with the atypical antidepressant tianeptine attenuates sickness behavior induced by peripheral but not central lipopolysaccharide and interleukin-1beta in the rat. **Psychopharmacology** (**Berlim)**, v. 154, n. 1, p. 50- 60, 2001.

CASTANON, N.; LEONARD, B. E.; NEVEU, P. J.; YIRMIYA, R. Effects of antidepressants on cytokine production and actions. **Brain Behavior Immunology**, v. 16, n. 5, p. 569-74, 2002.

CATTANEO, A.; GENNARELLI, M.; UHER, R.; BREEN, G.; FARMER, A.; AITCHISON, K. J.; CRAIG, I. W.; ANACKER, C.; ZUNSZTAIN, P. A.; MCGUFFIN, P.; PARIANTE, C. M. Candidate Genes Expression Profile Associated with Antidepressants Response in the Gendep Study: Differentiating between Baseline 'Predictors' and Longitudinal 'Targets'. **Neuropsychopharmacology**, v. 38, n. 3, p. 377-385, 2013.

CHEN, G. Y.; SHAW, M. H.; REDONDO, G; NÚÑEZ, G. The innate immune receptor Nod1 protects the intestine from inflammation-induced tumorigenesis. **Cancer Research**, v. 68, p. 10060- 10067, 2008.

CHENG, K. I.; WANG, H. C.; CHANG, L. L. Pretreatment with intrathecal amitriptyline potentiates anti-hyperalgesic effects of post-injury intra-peritoneal amitriptyline following spinal nerve ligation. **Biomed Central Neurology**, v. 12, n. 44, 2012.

CHIBA, T. Cell kinetics of carcinoma originating from rat colitis induced by dextran sulphate sodium. **Nippon Shokakibyo Gakkai Zasshi**, v. 90, p. 774-781, 1993.

CLAPPER, M. L.; COOPER, H. S.; CHANG, W. C. Dextran sulfate sodium-induced colitis-associated neoplasia: a promising model for the development of chemo preventive interventions. **Acta Pharmacology Sinica**, v. 28, n. 9, p. 1450-1459, 2007.

CODARRI, L.; FONTANA, A.; BECHER, B. Cytokine networks in multiple sclerosis: lost in translation. **Current Opinion Neurology**, v. 23, p. 205- 211, 2010.

COHN, D. W.; KINOSHITA, D.; PALERMO-NETO, J. Antidepressants prevent hierarchy destabilization induced by lipopolysaccharide administration in mice: a neurobiological approach to depression. **Annals of the New York Academy of Sciences**, v. 1262, p. 67-73, 2012.

COMINELLI, F.; NAST, C. C.; CLARK, B. D.; SCHINDLER, R.; LIERENA, R.; EYSSELEIN, V. E.; THOMPSON, R. C.; DINARELLO, C. A. Interleukin 1 (IL-1) gene expression, synthesis, and effect of specific IL-1 receptor blockade in rabbit immune complex colitis. **Journal of Clinical Investigation**, v. 86, n. 3, p. 972- 980, 1990.

CONNOR, T. J.; KELLY, J. P.; LEONARD, B. E. The effect of acute desipramine treatment on immunological parameters in the rat. **Medicine Science Research**, v. 25, p. 209-211, 1997.

CONNOR, T. J.; HARKIN, A.; KELLY, J. P.; LEONARD, B. E. Olfactory bulbectomy provokes a suppression of interleukin-1beta and tumour necrosis factoralpha production in response to an in vivo challenge with lipopolysaccharide: effect of chronic desipramine treatment. N**euroimmunomodulation** , v. 7, p. 27–35, 2000.

CONTI, A. C.; CRYAN, J. F.; DALVI, A.; LUCKI, I.; BLENDY, J. A. cAMP response element-binding protein is essential for the upregulation of brain-derived neurotrophic factor transcription, but not the behavioral or endocrine responses to antidepressant drugs. **Journal Neuroscience**, v. 22, p. 3262- 3268, 2002.

COOPER, H. S.; MURTHY, S. N.; SHAH, R. S.; SEDERGRAN, D. J. Clinicopathologic study of dextran sulfate sodium experimental murine colitis. **Laboratory Investigation**, v. 69, n. 2, p. 238- 249, 1993.

COOPER, H. S.; MURTHY, S.; KIDO, K.; YOSHITAKE, H.; FLANIGAN, A. Dysplasia and cancer in the dextran sulfate sodium mouse colitis model. Relevance to colitis-associated neoplasia in the human: a study of histopathology, B-catenin and p53 expression and the role of inflammation. **Carcinogenesis**, v. 21, n. 4, p. 757- 768, 2000.

COPPEN, A. The biochemistry of affective disorders. **British Journal of Psychiatry**, v. 113, p. 1237- 1264, 1967.

CORDERO, M. D.; SÁNCHEZ-ALCÁZAR, J. A.; BAUTISTA-FERRUFINO, M. R.; CARMONA-LÓPEZ, M. I.; ILLANES, M.; RÍOS, M. J.; GARRIDO-MARAVER, J.; ALCUDIA, A.; NAVAS, P.; DE MIGUEL, M. Acute oxidant damage promoted on cancer cells by amitriptyline in comparison with some common chemo therapeutic drugs. **Anticancer Drugs**; v. 21, p. 932- 944, 2010.

COSNES, J. Tobacco and IBD: relevance in the understanding of disease mechanisms and clinical practice. **Best Practice & Research Clinical Gastroenterology**, v. 18, n. 3, p. 481-96, 2004.

COSTA-PINTO, F. A.; BASSO, A. S.; BRITTO, L. R.; MALUCELLI, B. E.; RUSSO, M. Avoidance behavior and neural correlates of allergen exposure in a murine model of asthma. **Brain Behavior Immunogy**, v. 19, n. 1, p. 52-60, 2005.

COSTA-PINTO, F. A.; PALERMO-NETO, J. Neuroimmune interactions in stress. **Neuroimmunomodulation**, v. 17, n. 3, p. 196- 199, 2010.

COTRAN, R. S.; KUMAR, V.; COLLINS, T. **Pathologic basis of disease.** 6. ed. USA: W. B. Saunders Company: 1999.

CRYAN, J. F.; MARKOU, A.; LUCKI, I. Assessing antidepressant activity in rodents: recent developments and future needs. **Trends Pharmacology Science**, v. 23, p. 238-245, 2002.

CRYAN, J. F.; KELLY, P. H.; NEIJT, H. C.; SANSIG, G.; FLOR, P. J.; VAN DER PUTTEN, H. Antidepressant and anxiolytic-like effects in mice lacking the group III metabotropic glutamate receptor mGluR7. **European Journal of Neuroscience,** v. 17, p. 2409- 2417, 2003.

CRYAN, J. F.; MOMBEREAU, C.; VASSOUT, A. The tail suspension test as a model for assessing antidepressant activity: Review of pharmacological and genetic studies in mice. **Neuroscience and Biobehavioral Reviews**, v. 29, p. 571- 625, 2005.

CROHN, B. B.; GINZBURG, L.; OPPENHEIMER, G. D. Regional ileitis: a pathologic and clinical entity. **JAMA**, v. 99, p. 1323- 1329, 1932.

CUONG, D. T.; KATSIKEROS, R.; ABIMOSLEH, S. M. Current and novel treatments. In: SHENNAK, M. M. **Ulcerative colitis from genetics to complications**, 2012. Cap. 12, p. 189-223, 2012.

DALVI, A.; LUCKI, I. Murine models of depression. **Psychopharmacology**, v. 147, p. 14-16, 1999.

DANIELSON, T. J. Monoamine oxidase inhibitors and tricyclic antidepressants. In: MOZAYANI, A.; RAYMON, L. P. **Handbook of drug interactions**- a clinical and forensic guide. Totowa, New Jersey: Humana Press, 2004. Cap. 4, p. 149-173.

DANTZER, R. Innate immunity at the forefront of psychoneuroimmunology. **Brain, Behavior, and Immunity**, v. 18, p. 1 –6, 2004.

DANTZER, R.; KELLEY, K. W. Twenty years of research on cytokine-induced sickness behavior. **Brain Behavior Immunology**, v. 21, n. 2, p.153- 60, 2007.

DAVID, D. J.; NIC DHONNCHADHA, B. A.; JOLLIET, P.; HASCOET, M.; BOURIN, M. Are there gender differences in the temperature profile of mice after acute antidepressant administration and exposure to two animal models of depression? **Behavioural Brain Research**, v. 119, p. 203–211, 2001.

DELEPLANQUE, B.; NEVEU P. J. Immunological effects of neuropsyckiatric substances. In: GUENOUNOU, M. (Ed.). **Forum on immunomodulators.** Paris: John Libbey Eurotext, 1995. p. 287-302.

DENTENER, M. A.; BAZIL, V.; VON ASMUTH, E. J.; CESKA, M.; BUURMAN, W. A. Involvement of CD14 in lipopolysaccharide-induced tumor necrosis factor-alpha, IL-6 and IL-8 release by human monocytes and alveolar macrophages. **Journal of Immunology**, v. 150, p. 2885- 2891, 1993.

DE PAULA, V. F.; RIBEIRO, A.; PINHEIRO, M. L.; SAKAI, M.; LACAVA, M. C.; LAPACHINSKE, S. F.; MOREAU, R. L.; PALERMO-NETO, J. Methylenedioxymethamphetamine (Ecstasy) decreases neutrophil activity and alters leukocyte distribution in bone marrow, spleen and blood. **Neuroimmunomodulation**, v. 16, n. 3, p. 191-200, 2009.

DE SCHEPPER, H. U.; DE MAN, J. G.; MOREELS, T. G.; PELCKMANS, P. A.; DE WINTER, B. Y. Functional gut disorders and inflammatory bowel disease : comorbidity and clinical challenges. **Practical Gastroenterology**, v. 32, n. 1, p. 10- 17 2008.

DE SOUZA, M. M.; BELASCO, A. G. S.; AGUILAR- NASCIMENTO, J. E. Perfil epidemiológico dos pacientes portadores de doença inflamatória intestinal do estado de Mato Grosso. **Revista Brasileira de Coloproctologia**, v. 28, n. 3, p. 324- 328, 2008.

DEL REY, A.; BESEDOVSKY, H. O. Sympathetic nervous system-immune interactions in autoimmune lymphoproliferative diseases. **Neuroimmunomodulation**, v. 15, n. 1, p. 29-36, 2008.

DHABHAR, F. S. Stress-induced enhancement of cell-mediated immunity. **Annals New York Academic Science**, v. 840, p. 359-372, 1998.

DHABHAR, F. S.; MCEWEN, B. S. Enhancing versus suppressive effects of stress hormones on skin immune function. **Proceedings of the National Academy of Sciences of the United States of America**, v. 96, p. 1059-1064, 1999.

DIAMOND, M.; KELLY, J. P.; CONNOR, T. J. Antidepressants suppress production of the Th1 cytokine interferon-gamma, independent of monoamine transporter blockade. **European Neuropsychopharmacology**, v. 16, p. 481- 490, 2006.

DIAZ-GRANADOS, N.; HOWE, K.; LU, J.; MCKAY, D. M. Dextran sulfate sodium-induced colonic histopathology, but not altered epithelial ion transport, is reduced by

inhibition of phosphodiesterase activity. **American Journal of Pathology**, v. 156, n. 6, p. 2169- 2177, 2000.

DIELEMAN, L. A.; RIDWAN, B. U.; TENNYSON, G. S.; BEAGLEY, K. W.; BUCY, R. P.; ELSON, C. O. Dextran sulfate sodium-induced colitis occurs in severe combined immunodeficient mice. **Gastroenterology**, v. 107, n. 6, p. 1643-1652, 1994.

DIELEMAN, L. A.; PALMEN, M. J.; AKOL, H.; BLOEMENA, E.; PEÑA, A. S.; MEUWISSEN, S. G.; VAN REES, E. P. Chronic experimental colitis induced by dextran FELTEN, S. Y.; OLSCHOWKA, J. A. Noradrenergic sympathetic innervations of the spleen: II. Tyrosine hydroxylase (TH)-positive nerve terminal form synaptic-like contact on lymphocytes in the splenic white pulp. **Journal of Neuroscience Research**, v. 18, p. 37–48, 1987.

DUNN, E.; BROWN, C.; LOVE, B. Decreasing anxiety. **Journal Health Care Mark**, v. 15, n. 1, p. 21-23, 1995.

EISEN, J., IRWIN, J., QUAY, J., LIVNAT, S. The effect of antidepressants on immune function in mice. **Biology Psychiatry**, v. 26, p. 805- 817, 1989.

EL YACOUBI, M.; BOUALI, S.; POPA, D.; NAUDON, L.; LEROUX-NICOLLET, I.; HAMON, M.; COSTENTIN, J.; ADRIEN, J.; VAUGEOIS, J. M. Behavioral, neurochemical, and electrophysiological characterization of a genetic mouse model of depression. **Proceedings of the National Academy of Sciences of the United States of America**, v. 100, p. 6227–6232, 2003.

ELENKOV, I. J.; WILDER, R. L.; CHROUSOS, G. P.; VIZI, E. S. The sympathetic nerve: an integrative interface between two supersystems: the brain and the immune system. **Pharmacology Review**, v. 52, p. 595- 638, 2000.

ELLSWORTH- BOWERS, E. R.; CORWIN, E. J. Nutrition and the psychoneuroimmunology of postpartum depression. **Nutrition Research Reviews**, v. 25, n. 1, p. 180- 192, 2012.

ELSON, C. O.; SARTOR, R. B.; TENNYSON, G. S.; RIDDELL, R. H. Experimental models of inflammatory bowel disease. **Gastroenterology**, v. 109, p. 1344-1367, 1995.

FERRAZ-DE-PAULA, V.; RIBEIRO, A.; SOUZA-QUEIROZ, J.; PINHEIRO, M. L.; VECINA, J. F.; SOUZA, D. P.; QUINTEIRO-FILHO, W. M.; MOREAU, R. L.; QUEIROZ, M. L.; PALERMO-NETO, J. 3,4-methylenedioxymethamphetamine (MDMA--Ecstasy) decreases neutrophil activity through the glucocorticoid pathway and impairs host resistance to Listeria monocytogenes infection in mice. **Journal Neuroimmune Pharmacology**, v. 9, n. 5, p. 690-702, 2014.

FLANIGAN, M. J.; ACCONE, Q.; LABURN, H. P. Amitriptyline attenuates the febrile response to a pyrogen in rabbits. **Journal Basic Clinical Physiology Pharmacology**, v. 3, p. 19–32, 1992.

FONSECA, E. S.; MASSOCO, C. O.; PALERMO-NETO, J. Effects of prenatal stress on stress-induced changes in behavior and macrophage activity of mice. **Physiology Behavior**, v. 77, n. 2-3, p. 205-215, 2002.

FORTIN, M.; DUBOIS, M. F.; HUDON, C.; SOUBHI, H.; ALMIRALL, J. Multimorbidity and quality of life: a closer look. **Health Quality Life Outcomes**, v. 5, n. 52, p. 1- 8, 2007.

FORT, M.; LESLEY, R.; DAVIDSON, N.; MENON, S.; BROMBACHER, F.; LEACH, M.; RENNICK, D. L-4 exacerbates disease in a Th1 cell transfer model of colitis. **Journal of Immunology**, v. 166, p. 2793–2800, 2001.

FOSTER, B. C.; GALLICANO, K. D.; WHITEHOUSE, L. W.; MCGILVERAY, I. J.; KHAN, S. R. Dextran sulfate disposition in the rat. **Biopharmaceutics & Drug Disposition**, v. 11, n. 7, p. 595-606, 1990.

FREDMAN, L.; CAULEY, J. A.; HOCHBERG, M.; ENSRUD, K. E.; DOROS, G. Mortality associated with caregiving, general stress, and caregiving-related stress in elderly women: results of caregiver-study of osteoporotic fractures. **Journal of the American Geriatrics Society**, v. 58, n. 5, p. 937- 943, 2010.

FRYER, J. D.; LUKAS, R. J. Antidepressants noncompetitively inhibit nicotinic acetylcholine receptor function. **Journal of Neurochemistry**, v.72, n. 3, p. 1117- 1124, 1999.

FUCHS, B. A.; ALBRIGHT, J. W.; ALBRIGHT, J. F. Adrenergic receptors on murine lymphocytes: density varies with cell maturity and lymphocyte subtype and is decreased after antigen administration. **Cellular Immunology**, v. 243, p. 495–508, 1986.

FUNDERBURG, N. T.; STUBBLEFIELD PARK, S. R.; SUNG, H. C.; HARDY, G.; CLAGETT, B.; IGNATZ-HOOVER, J.; HARDING, C. V.; FU, P.; KATZ, J. A.; LEDERMAN, M. M.; LEVINE, A. D. Circulating CD4(+) and CD8(+) T cells are activated in inflammatory bowel disease and are associated with plasma markers of inflammation. **Immunology**, v. 140, n. 1, p. 87- 97, 2013.

GAFFEN, S. L.; JAIN, R.; GARG, A.V.; CUA, D. J. The IL-23–IL-17 immune axis: from mechanisms to therapeutic testing. **Nature Reviews Immunology**, v. 14, p. 585-600, 2014.

GASPARRINI, M.; RIVAS, D.; ELBAZ, A.; DUQUE, G. Differential expression of cytokines in subcutaneous and marrow fat of aging C57BL/6J mice. **Experimental Gerontology**, v. 44, p. 613-618, 2009.

GAUDIO, E.; TADDEI, G.; VETUSCHI, A.; SFERRA, R.; FRIERI, G.; RICCIARDI, G.; CAPRILLI, R. Dextran sulfate sodium (DSS) colitis in rats: clinical, structural and ultra structural aspects. **Digestive Diseases and Sciences**, v. 44, p. 1458- 1475, 1999.

GEBOES, K.; COLLINS, S. Structural abnormalities of the nervous system in Crohn's Disease and Ulcerative Colitis. **Neurogastroenterology & Motility**, v. 10, n. 3, p. 189-202, 1998.

GEBBOES, K.; DALLE, I. Influence of treatment on morphological features of mucosal inflammation. **Gut**, v. 50, p. iii37- iii42, 2002, Suplement, III.

GEIER, M. S.; TENIKOFF, D.; YAZBECK, R.; MCCAUGHAN, G. W.; ABBOTT, C. A.; HOWARTH, G. S. Development and resolution of experimental colitis in mice with targeted deletion of dipeptidyl peptidase IV. **Journal of Cellular Physiology**, v. 204, n. 2, p. 687- 692, 2005.

GERSON, L. B.; TRIADAFILOPOULOS, G. Palliative care in inflammatory bowel disease: an evidence-based approach. **Inflammatory Bowe Disease**, v. 6, n. 3, p. 228- 243, 2000.

GHIA, J. E.; GALEAZZI, F.; FORD, D. C.; HOGABOAM, C. M.; VALLANCE, B. A.; COLLINS, S. Impaired parasympathetic function increases susceptibility to inflammatory bowel disease in a mouse model of depression. **Journal of Clinical Investigation**, v. 118, n. 6, p. 2209-2218, 2008.

GHIA, J. E.; GALEAZZI, F.; FORD, D. C. et al. Role of M-Csf-dependent macrophages in colitis is driven by the nature of the inflammatory stimulus. **American Journal of Physiology - Gastrointestinal and Liver Physiology**, v. 294, p. G770–G77, 2008.

GHIA, J. E.; BLENNERHASSETT, P.; DENG, Y.; VERDU, E. F.; KHAN, W. I.; COLLINS, S. M. Reactivation of inflammatory bowel disease in a mouse model of depression. **Gastroenterology**, v. 136, n. 7, p. 2280- 2288, 2009.

GHIA, J. E.; PARK, A. J.; BLENNERHASSETT, P.; KHAN, W. I.; COLLINS, S. M. Adoptive transfer of macrophage from mice with depression-like behavior enhances susceptibility to colitis. **Inflammatory Bowel Disease**, v. 17, n. 7, p. 1474- 1489, 2011.
GOLDSTEIN, B. I.; KEMP, D. E.; SOCZYNSKA, J. K.; MCINTYRE, R. S. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. **Journal Clinical Psychiatry**, v. 70, p. 1078-1090, 2009.

GOUGH, D. J.; LEVY, D. E.; JOHNSTONE, R. W.; CLARKE, C. J. IFN gamma signaling-does it mean JAK-STAT? **Cytokine Growth Factor Review**, v. 19, p. 383–394, 2008.

GRAFF, L. A.; WALKER, J. R.; BERNSTEIN, C. N. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. **Inflammatory Bowel Disease**, v. 15, n. 7, p. 1105- 1118, 2009.

GRIFFIN, M. G; MINER, P. B. Review article: refractory distal colitis explanations and options. **Aliment Pharmacology and Therapeutics**, v. 10, p. 39- 48, 1996.

GRIMM, M. C.; PULLMAN, W. E.; BENNETT, G. M.; SULLIVAN, P. J.; PAVLI, P.; DOE, W. F. Direct evidence of monocyte recruitment to inflammatory bowel disease mucosa. **Journal of Gastroenterology and Hepatology**, v. 10, n. 4, p. 387- 395, 1995.

GROSS, V.; ANDUS, T.; LESER, H. G.; ROTH, M.; SCHÖLMERICH, J. Inflammatory mediators in chronic inflammatory bowel diseases. **Journal klinische Wochenschrift**, v. 15, n. 69, p. 981- 987, 1991. Supplement, 21-23.

_____. Evidence for continuous stimulation of interleukin-6 production in Crohn's disease. **Gastroenterology**, v. 102, p. 514 –519, 1992.

GUEMEI, A. A.; EL DIN, N. M.; BARAKA, A. M.; EL SAID DARWISH, I. Do desipramine [10,11-dihydro-5-[3-(methylamino) propyl]-5H-dibenz[b,f]azepine monohydrochloride] and fluoxetine [N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]-propan-1-amine] ameliorate the extent of colonic damage induced by acetic acid in rats? **Journal of Pharmacology and Experimental Therapeutics**, v. 27, n. 3, p. 846-850, 2008.

GURGEL, J. A.; LIMA-JÚNIOR, R. C.; RABELO, C. O.; PESSOA, B. B.; BRITO, G. A.; RIBEIRO, R. A. Amitriptyline, Clomipramine, and Maprotiline Attenuate the Inflammatory Response by Inhibiting Neutrophil Migration and Mast Cell Degranulation. **Revista Brasileira de Psiquiatria**, v. 35, n. 4, p. 387- 392, 2013.

HAJHASHEMI, V.; MINAIYAN, M.; EFTHEKHARI, M. Anti-Inflammatory activity of a selection of antidepressant drugs. **Iranian Journal of Pharmaceutical Sciences**, v. 4, n. 3, p. 225-300, 2008.

HAJHASHEMI, V.; SADEGHI, H.; MINAIYAN, M.; MOVAHEDIAN, A.; TALEBI, A. The Role of central mechanisms in the anti-inflammatory effect of amitriptyline on carrageenan-induced paw edema in rats. **Clinics**, v. 65, n. 11, p. 1183-1187, 2010.

HALL, H.; OGREN, S. Effects of antidepressant drugs on different receptors in the brain. **European Journal of Pharmacology**, v. 70, p. 393-407, 1981.
HALL, S. W.; COOKE, A. Autoimmunity and inflammation: murine models and translational studies. **Mammalian Genome**, v. 22, p. 377–389, 2011.

HAMASATO, E. K.; DE LIMA, A. P.; DE OLIVEIRA, A. P.; DOS SANTOS FRANCO, A. L.; DE LIMA, W. T.; PALERMO-NETO, J. Cohabitation with a sick partner increases allergic lung inflammatory response in mice. **Brain Behavavior Immunogy**, v. 42, p. 109-117, 2014.

HACKAM, D. G.; REDELMEIER, D. A. Translation of research evidence from animals to humans. **JAMA**, v. 296, p. 1731-1732, 2006.

HARMER, C. J.; BHAGWAGAR, Z.; PERRETT, D. I.; VÖLLM, B. A.; COWEN, P. J.; GOODWIN, G. M. Accute SSRI administration affects theprocessing of social cues in healthy volunteers. **Neuropsychopharmacology**, v. 28, p. 148–152, 2003a.

HARMER, C. J.; HILL, S. A.; TAYLOR, M. J.; COWEN, P. J.; GOODWIN, G. M. Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. **American Journal of Psychiatry**, v. 160, p. 990–992, 2003b.

HASHIOKA, S.; KLEGERIS, A.; MONJI, A.; KATO, T.; SAWADA, M.; MCGEER, P. L.; KANBA, S. Antidepressants inhibit interferon-gamma-induced microglial production of IL-6 and nitric oxide. **Experimental Neurology**, n. 1, p. 33-42, 2007.

HEALY, D. **The antidepressant era**. Cambridge: Harvard University Press, 1997.

HENDRICKSON, B. A.; GOKHALE, R.; CHO, J. H. Clinical Aspects and pathophysiology of inflammatory bowel disease**. Clinical Microbiology Reviews**, v. 15, n. 1, p. 79-94, 2002.

HERBERT, T. B.; COHEN, S. Depression and immunity: a meta-analytic review. **Psychological Bulletin,** v. 113, p. 472- 486, 1993.

HERBERTH, G.; WEBER, A.; RÖDER, S.; ELVERS, H. D.; KRÄMER, U.; SCHINS, R. P.; DIEZ, U.; BORTE, M.; HEINRICH, J.; SCHÄFER, T.; HERBARTH, O.; LEHMANN, I.; LISAPLUS STUDY GROUP. Relation between stressful life events, neuropeptides and cytokines: results from the LISA birth cohort study. **Pediatric Allergy and Immunology**, v. 19, n. 8, p. 722-729, 2008.

HELZER, J. E.; CHAMMAS, S.; NORLAND, C. C.; STILLINGS, W. A.; ALPERS, D. H. A study of the association between Crohn's disease and psychiatric illness. **Gastroenterology**, v. 86, n. 2, p. 324-330, 1984.

HICKIE, L.; LLOYD, A. Are cytokines associated with neuropsychiatric syndromes in humans? **International Journal of Immunopharmacology**, v. 17, n. 8, p. 677- 683, 1995.

HILES, S. A.; BAKER, A. L.; DE MALMANCHE T, ATTIA, J. Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis. **Psychology Medicine**, v. 16, p. 1-12, 2012.

HIMMERICH, H.; BINDER, E. B.; KÜNZEL, H. E.; SCHULD, A.; LUCAE, S.; UHR, M.; POLLMÄCHER, T.; HOLSBOER, F.; ISING, M. Successful antidepressant therapy restores the disturbed interplay between TNF-alpha system and HPA axis. **Biology Psychiatry**, v. 60, p. 882–888, 2006.

HINZE-SELCH, D.; SCHULD, A.; KRAUS, T.; KÜHN, M.; UHR, M.; HAACK, M.; POLLMÄCHER, T. Effects of antidepressants on weight and on the plasma levels of leptin, TNF-alpha and soluble TNF receptors: a longitudinal study in patients treated with amitriptyline or paroxetine. **Neuropsychopharmacology**, v. 23, p. 13-19, 2000.

HIRATA, I.; MURANO, M.; NITTA, M.; SASAKI, S.; TOSHINA, K.; MAEMURA, K.; KATSU, K. Estimation of mucosal inflammatory mediators in rat DSS-induced colitis. Possible role of PGE(2) in protection against mucosal damage. **Digestion**, v. 63, n. 1, p. 73-80, 2001.

HOIE, O.; WOLTERS, F. L.; RIIS, L.; BERNKLEV, T.; AAMODT, G.; CLOFENT, J.; TSIANOS, E.; BELTRAMI, M.; ODES, S.; MUNKHOLM, P.; VATN, M.; STOCKBRÜGGER, R. W.; MOUM, B. Low colectomy rates in ulcerative colitis in an unselected european cohort followed for 10 years. **Gastroenterology**, v. 132, n. 2, p. 507-515, 2007.

HOLSBOER, F.; BARDEN, N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. **Endocrinology Reviews**, v. 17, p. 187-205, 1996.

HUANG, H.; PATEL, D. D.; MANTON, K. G. The immune system in aging: roles of

cytokines, T cells and NK cells. **Frontiers in Bioscience**, v. 10, p. 192- 215, 2005.

HUANG, W.; JIANG, S. M.; JIA, L.; You, L. Q.; Huang, Y. X.; Gong, Y. M.; Wang, G. Q. Effect of amitriptyline on gastrointestinal function and brain-gut peptides: a double-blind trial. **World journal of gastroenterology**, v. 19, n. 26, p. 4214- 4220, 2013.

HYAMS, J. S.; FITZGERALD, J. E.; TREEM, W. R.; WYZGA, N.; KREUTZER, D. L. Relationship of functional and antigenic interleukin 6 to disease activity in inflammatory bowel disease. **Gastroenterology**, v. 104, p. 1285- 1292, 1993.

ISHIOKA, T.; KUWABARA, N.; OOHASHI, Y.; WAKABAYASHI, K. Induction of colorectal tumors inrats by sulfated polysaccharides. **Critical Reviews in Toxicology**, v. 17, n. 3, p. 215- 244, 1987.

ICHINOSE, M.; BARNES, P. J. Cytokine-directed therapy in asthma. **Current Drug Targets Inflammatory Allergy**, v. 3, p. 263–269, 2004.

IWANAGA, T.; HOSHI, O.; HAN, H.; FUJITA, T. Morphological analysis of acute ulcerative colitis experimentally induced by dextran sulfate sodium in the guinea pig: Some possible mechanisms of cecal ulceration. **Journal of Gastroenterology**, v. 29, n. 4, p. 430-438, 1994.

JANSSEN, D. G.; CANIATO, R. N.; VERSTER, J. C.; BAUNE T. A. A Psychoneuroimmunological Review on Cytokines Involved in Antidepressant Treatment Response. **Human Psychopharmacology**, v. 25, n. 3, p. 201- 215, 2010.

JIANG, C. L.; LU, C. L.; LIU, X. Y. The molecular basis for bidirectional communication between the immune and neuroendocrine systems. **Domestic Animal Endocrinology**, v. 15, p. 363–369, 1998.

JIANG, H. R.; GILCHRIST, D. S.; POPOFF, J. F.; JAMIESON, S. E.; TRUSCOTT, M.; WHITE, J. K.; BLACKWELL, J. M. Influence of Slc11a1 (Formerly Nramp1) on Dss-induced colitis in mice. **Journal of Leukocytes Biology**, v. 85, n. 4, p. 703- 10, 2009.

JIWA, M.; MITCHELL, G.; SIBBRIT, D.; GIRGIS, A.; BURRIDGE, L. Addressing the needs of caregivers of cancer patients in general practice: a complex intervention. **Quality in Primary Care**, v. 18, n. 1, p. 9-16, 2010.

JOHANSSON, M. E.; GUSTAFSSON, J. K.; SJÖBERG, K. E. Bacteria penetrate the inner mucus layer before inflammation in the dextran sulfate colitis model. **PLoS One**, v. 5, n. 8, e. 12238, p. 1-9; 2010.

KAGAYA, A.; KUGAYA, A.; TAKEBAYASHI, M.; FUKUE-SAEKI, M.; SAEKI, T.; YAMAWAKI, S.; UCHITOMI, Y. Plasma concentrations of interleukin-1beta, interleukin-6, soluble interleukin-2 receptor and tumor necrosis factor alpha of depressed patients in Japan. **Neuropsychobiology**, v. 43, p. 59- 62, 2001.

KAMEI, J.; MIYATA, S.; MORITA, K.; SAITOH, A.; TAKEDA, H. Effects of selective

serotonin reuptake inhibitors on immobility time in the tail suspension test in streptozotocin-induced diabetic mice. **Pharmacology Biochemistry and Behavior**, v. 75, p. 247-254, 2003.

KATZ, M. M.; KOSLOW, S. H.; MAAS, J. W.; FRAZER, A.; BOWDEN, C. L.; CASPER, R.; CROUGHAN, J.; KOCSIS, J.; REDMOND, JR. E. The timing, specificity and clinical prediction of tricyclic drug effects in depression. **Psychological Medicine**, v. 17, p. 297- 309, 1987.

KASER, A.; ZEISSIG, S.; BLUMBERG, R. S. Inflammatory bowel disease. **Annual Review of Immunology**, v. 28, p. 573-621, 2010.

KAST, R. E. Anti- and pro-inflammatory considerations in antidepressant use during medical illness: bupropion lowers and mirtazapine increases circulating tumor necrosis factor-alpha levels. **General Hospital Psychiatry**, v. 25, p. 495- 496, 2003.

KATAYAMA, K.; WADA, K.; NAKAJIMA, A.; MIZUGUCHI, H.; HAYAKAWA, T.; NAKAGAWA, S.; KADOWAKI, T.; NAGAI, R.; KAMISAKI, Y.; BLUMBERG, R. S.; MAYUMI, T. A novel PPAR gamma gene therapy to control inflammation associated with inflammatory bowel disease in a murine model. **Gastroenterology**, v. 124, n. 5, p. 1315-1324, 2003.

KENIS, G.; MAES, M. Effects of antidepressants on the production of cytokines. **International Journal of Neuropsychopharmacology**, v. 5, n. 4, p. 401- 412, 2002.

KHAN, W. I.; MOTOMURA, Y.; WANG, H.; EL-SHARKAWY, R. T.; VERDU, E. F.; VERMA-GANDHU, M.; ROLLINS, B. J.; COLLINS, S. M. Critical role of MCP-1 in the pathogenesis of experimental colitis in the context of immune and enterochromaffin cells. **American Journal of Physiology- Gastrointestinal and Liver Physiology**, v. 291, n. 5, p. G803-G811, 2006.

KIRSNER, J. B.; ELCHLEPP, J. The production of an experimental ulcerative colitis in rabbits. **Transactions of the Association of American Physicians**, v. 70, p. 102- 119, 1957.

KITAJIMA, S.; MORIMOTO, M.; SAGARA, E. A model for dextran sodium sulfate (DSS)-induced mouse colitis: bacterial degradation of DSS does not occur after incubation with mouse cecal contents. **Experimental Animals**, v. 51, n. 2, p. 203- 206, 2002.

KITAJIMA, S.; TAKUMA, S.; MORIMOTO, M. Tissue distribution of dextran sulfate sodium (dss) in the acute phase of murine DSS-induced colitis. **Journal Veterinary Medicine Science**, v. 61, n.1, p. 67-70, 1999.

_____. Histological analysis of murine colitis induced by dextran sulfate sodium of different molecular weights. **Experimental Animals**, v. 49, n. 1, p. 9-15, 2000.

KOBOZIEV, I.; KARLSSON, F.; ZHANG S.; GRISHAM, M. B. Pharmacological Intervention studies using mouse models of the inflammatory bowel diseases: translating preclinical data into new drug therapies. **Inflammatory Bowel Disease**, v. 17, n. 5, p. 1229-1245, 2011.

KOH, S. J.; KIM, J. M.; KIM, I. K.; KIM, N.; JUNG, H. C.; SONG, I. S.; KIM, J. S. Fluoxetine inhibits NF-κB signaling in intestinal epithelial cells and ameliorates experimental colitis and colitis-associated colon cancer in mice. **Gastrointestinal and Liver Physiology**, v. 301, n. 1, p. G9- G19, 2011.

KORNHUBER, J.; HENKEL, A. W.; GROEMER, T. W.; STÄDTLER, S.; WELZEL, O.; TRIPAL, P.; ROTTER, A.; BLEICH, S.; TRAPP, S. Lipophilic cationic drugs increase the permeability of lysosomal membranes in a cell culture system. **Journal of Cellular Physiology**, v. 224, n.1, p. 152-164, 2010.

KOYAMA, H.; IWAI, A.; IWASHITA, E.; TOKUNAGA, T.; SASAKI, J.; MASTUDA, K.; SHITAYA, M.; KAWAGUCHI, A.; NAGAO, S.; MIYAHARA, T.; HINO, K.; NIWA, H. Experimental colitis in rats resembling human ulcerative colitis (in Japanese). **Gastroenteroly Endoscopy**, v. 37, p. 1584-1593, 1992.

KREYDIYYEH, S. I.; AL-SADI, R. The mechanism by which interleukin-1 beta reduces net fluid absorption from the rat colon. **European Cytokine Network**, v. 13, n. 3, p. 358- 363, 2002.

KUBERA, M.; BASTA-KAIM, A.; SKOWRON-CENDRZAK, A.; MAZUR-KOLECKA, B.; ROMAN, A.; BORYCZ, J. Effect of repeated amitriptyline administration to mice on the T lymphocyte proliferative activity and natural killer cell cytotoxicity. **Polish Journal Pharmacology**, v. 47, p. 321- 326, 1995.

KUBERA, M.; MAES, M. Serotonin-immune interactions in major depression. In: PETTERSON, P.; KORDON, C.; CHRISTEN, Y. (Ed.). **Neuro-immune interactions in neurologic and psychiatric disorders**. Berlim Heidelberg: Springer-Verlag, 2000. p. 79- 87.

KUBERA, M.; HOLAN, V.; MATHISON, R.; MAES, M. The effect of repeated amitriptyline and desipramine administration on cytokine release in C57BL/6 Mice. **Psychoneuroendocrinology**, v. 25, n. 8, p. 785– 797, 2000.

KUBERA, M.; KENIS, G.; BOSMANS, E.; KAJTA, M.; BASTA-KAIM, A.; SCHARPE, S.; BUDZISZEWSKA, B.; MAES, M. Stimulatory effect of antidepressants on the production of IL-6. **International Immunopharmacology**, v. 4, n. 2, p. 185- 192, 2004.

KUBERA, M.; LIN, A. H.; KENIS, G.; BOSMANS, E.; VAN BOCKSTAELE, D.; MAES, M. Anti-Inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. **Journal Clinical Psychopharmacology**, v. 21, p. 199- 206, 2001.

KUHN R. Geschichte der medikamentösen depression sbehandlung. In: **LINDE,** O. K. (Ed.). **Pharmakopsychiatrie im Wandel der Zeit.** Klingenmünster: Tilia-Verlag, 1988. p. 10-27.

KULLMANN, F.; MESSMANN, H.; ALT, M.; GROSS, V.; BOCKER, T.; SCHÖLMERICH, J.; RÜSCHOFF, J. Clinical and histopathological features of dextran sulfate sodium induced acute and chronic colitis associated with dysplasia in rats. **International Journal of Colorectal Disease**, v. 16, p. 238- 246, 2001.

KURINA, L. M.; GOLDACRE, M. J.; YEATES, D.; GILL, L. E. Depression and anxiety in people with inflammatory bowel disease. **Journal of Epidemiology and Community Health**, v. 55, n. 10, p. 716- 720, 2001.

KURTOVIC, J.; SEGAL, I. Recent advances in biological therapy for inflammatory bowel disease. **Tropical gastroenterology**, v. 25, p. 9-14, 2004.

KWON, K. H.; MURAKAMI, A.; HAYASHI, R.; OHIGASHI, H. Interleukin-1beta targets interleukin-6 in progressing Dextran sulfate sodium-induced experimental colitis. **Biochemical and Biophysical Research Communications**, v. 337, n. 2, p. 647- 654, 2005.

LAKHAN, S. E.; KIRCHGESSNER, A. Neuroinflammation in inflammatory bowel disease. **Journal of Neuroinflammation**, v. 7, n. 37, p. 1- 12, 2010.

LAMPINEN, M.; SANGFELT, P.; TAHA, Y.; CARLSON, M. Accumulation, activation, and survival of neutrophils in ulcerative colitis: regulation by locally produced factors in the colon and impact of steroid treatment. **International Journal of Colorectal Disease**, v. 23, p. 939–946, 2008.

LANDMANN, R.; SCHAUB, B.; LINK, S.; WACKER, H. R. Unaltered monocyte function in patients with major depression before and after three months of antidepressive therapy. **Biological Psychiatry**, v. 41, n. 6, p. 675- 81, 1997.

LANGER, G.; HEIMANN, H. E. **Psychopharmaka, grundlagen und therapie**. Viena-Nueva York: Springer-Verlag, 1983. p. 59-65.

LANQUILLON, S.; KRIEG, J. C.; BENING-ABU-SHACH, U.; VEDDER, H. Cytokine production and treatment response in major depressive disorder. **Neuropsychopharmacology**, v. 22, p. 370- 379, 2000.

LAPIN, J. P.; OXENKRUG, G. F. Intensification of the central serotonergic processes as a possible determinal of the thymoleptic effect. **The Lancet**, p. 132- 136, 1969.

LARMONIER, C. B.; MIDURA-KIELA, M. T.; RAMALINGAM, R.; LAUBITZ, D.; JANIKASHVILI, N.; LARMONIER, N.; GHISHAN, F. K.; KIELA, P. R. Modulation of neutrophil motility by curcumin: implications for inflammatory bowel disease. **Inflammatory Bowel Disease**, v. 17, n. 2, p. 503- 515, 2011.

LAZZARINI, R.; SAKAI, M.; COSTA-PINTO, F. A.; PALERMO-NETO, J. Diazepam decreases leukocyte-endothelium interactions in situ. **Immunopharmacology Immunotoxicology**, v. 32, n. 3, p. 402- 409, 2010.

LEE, J. C.; LYONS, P. A.; MCKINNEY, E. F.; SOWERBY, J. M.; CARR, E. J.; BREDIN, F.; RICKMAN, H. M.; RATLAMWALA, H.; HATTON, A.; RAYNER, T. F.; PARKES, M.; SMITH, K. G. Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn disease and ulcerative colitis. **Journal of Clinical Investigation**, v. 121, p. 4170-4179, 2011.

LEE, M. J.; LEE, J. K.; CHOI, J. W.; LEE, C. S.; SIM, J. H. Interleukin-6 induces S100A9 expression in colonic epithelial cells through STAT3 activation in experimental ulcerative colitis. **PLoS One**, v. 7, n. 9, p. e38801, 2012.

LEONARD, B. E. The immune system, depression and the action of antidepressants. **Program Neuropsychopharmacology Biology Psychiatry**, v. 25, n. 4, p. 767- 780, 2001.

LI, Z.; ARIJS, I.; DE HERTOGH, G.; VERMEIRE, S.; NOMAN, M.; BULLENS, D.; COOREVITS, L.; SAGAERT, X.; SCHUIT, F.; RUTGEERTS, P.; CEUPPENS, J. L.; VAN ASSCHE, G. Reciprocal changes of Foxp3 expression in blood and intestinal mucosa in IBD patients responding to infliximab. **Inflammatory Bowel Disease**, v. 16, n. 8, p. 1299- 1310, 2010.

LI, L.; LIU, Z.; YANG, X.; YAN, H.; BAO, S.; FEI, J. Bioluminescence Imaging for Il-1β Expression in Experimental Colitis. **Journal of Inflammatory**, v. 10, n. 1, p. 16, 2013.

LI, L.; GONG, C.; ZHAO, M.; FENG, B. Role of Interleukin-22 in Inflammatory Bowel Disease. **World Journal of Gastroenterology**, v. 20, n. 48, p. 8177- 8188, 2014.

LICINIO, J.; WONG, M. L. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. **Molecular Psychiatry**, v. 4, n. 4, p. 317- 327, 1999.

LIEBERMAN III, J. A. History of the use of antidepressants in primary care. **Primary Care Companion Journal of Clinical Psychiatry**, v. 5, n. 7, p. 6-10, 2003.

LIGEIRO-OLIVEIRA, A. P.; FIALHO DE ARAÚJO, A. M.; LAZZARINI, R.; SILVA, Z. L.; DE NUCCI, G.; MUSCARÁ, M. N.; TAVARES DE LIMA, W.; PALERMO-NETO, J. Effects of amphetamine on immune-mediated lung inflammatory response in rats. **Neuroimmunomodulation**, v. 11, n. 3, p. 181-190, 2004.

LIGNON, M. F.; BERNAD, N.; MARTINEZ, J. Pharmacological characterization of type B cholecystokinin binding sites on the human JURKAT T lymphocyte cell line. **Molecular Pharmacolology**, v. 39, n. 5, p. 615-620, 1991.

LIGUMSKY, M.; SIMON, P. L.; KARMELI, F.; RACHMILEWITZ, D. Role of interleukin 1 in inflammatory bowel disease--enhanced production during active disease. **Gut**, v. 31, n. 6, p. 686- 689, 1990.

LITTRELL, J. L. Taking the perspective that a depressive state reflects inflammation: implications for the use of antidepressants. **Frontiers in Psychology**, v. 3, p. 297, 2012.

LIU, X.; GERSHENFELD, H. K. Genetic differences in the tail-suspension test and its relationship to imipramine response among 11 inbred strains of mice. **Biological Psychiatry**, v. 49, p. 575- 581, 2001.

LOCKART-MUMMERY, H. E. Crohn's disease: anal lesions. **Disease Colon Rectum**, v. 18, n. 200, p. 282-293, 1975.

LÓPEZ-MUÑOZ, F.; ALAMO, C.; Historical evolution of the neurotransmission concept. **Journal Neural Transmission**, v. 116, n. 5, p. 515- 533, 2009.

LOUIS, E.; BELAICHE, J.; VAN KEMSEKE, C.; FRANCHIMONT, D.; DE GROOTE, D.; GUEENEN, V.; MARY, J. Y. A high serum concentrationof interleukin-6 is predictive of relapse in quiescent Crohn's disease. **European Journal of Gastroenterology & Hepatology**, v. 9, p. 939- 944, 1997.

LUCIN, K. M.; WYSS-CORAY, T. Immune activation in brain aging and neurodegeneration: too much or too little? **Neuron**, v. 64, n. 1, p.110-122, 2009.

LUDWICZEK, O.; VANNIER, E.; BORGGRAEFE, I.; KASER, A.; SIEGMUND, B.; DINARELLO, C. A.; TILG, H. Imbalance between interleukin-1 agonists and antagonists: relationship to severity of inflammatory bowel disease**. Clinical & Experimental Immunology**, v. 138, p. 323- 329, 2004.

MACHADO, T. R. M. **Alterações neuroimunes induzidas em camundongos machos pela convivência com um companheiro doente**. 2013. 147 f. Dissertação (Mestre em Ciências) - Faculdade de Medicina Veterinária e Zootecnia, Universidadede São Paulo, São Paulo, 2013.

MADDEN, K. S.; SANDERS, V. M.; FELTEN, D. L. Catecholamine influences and sympathetic neural modulation of immune responsiveness. **Annual Review of Pharmacology and Toxicology**, v. 35, p. 417- 448, 1995.

MAES, M.; SONG, C.; LIN, A-H.; KUBERA, M. In Vitro Immunoregulatory Effects of Lithium in Healthy Volunteers. **Psychopharmacology**, v. 143, p. 401- 407, 1999.

MAES, M ; VANDOOLAEGHE E.; VAN HUNSEL, F; BRIL, T.; DEMEDTS, P.; MAES, M. The immunoregulatory effects of antidepressants. **Human Psychopharmacology**, v. 16, p. 95–103, 2001.

MAESTRONI, G. Immunology needs the mind. **Nature Immunology**, v. 5, n. 8, p. 763, 2004.

MAHIDA, Y. R.; PATEL, S.; GIONCHETTI, P.; VAUX, D.; JEWELL, D. P. Macrophage subpopulations in lamina propria of normal and inflamed colon and terminal ileum. **Gut,** v. 30, p. 826- 834, 1989.

MAHIDA, Y. R.; WU, K.; JEWELL, D. P. Enhanced production of interleukin 1-beta by mononuclear cells isolated from mucosa with active ulcerative colitis of Crohn's disease. **Gut**, v. 30, n. 6, p. 835- 838, 1989.

MAHLER, M.; BRISTOL, I. J.; LEITER, E. H.; WORKMAN, A. E.; BIRKENMEIER, E. H.; ELSON, C. O.; SUNDBERG, J. P. Differential susceptibility of inbred mouse strains to dextran sulfate sodium-induced colitis. **American Journal of Physiology**, v. 274, n. 3, p. 544-551, 1998.

MARCHAND, F.; ARDID, D.; CHAPUY, E.; ALLOUI, A.; JOURDAN, D.; ESCHALIER, A. Evidence for an involvement of supraspinal delta- and spinal mu-opioid receptors in the antihyperalgesic effect of chronically administered clomipramine in mononeuropathic rats. **Journal of Pharmacology Experimental Therapeutics**, v. 307, n. 1, p. 268- 274, 2003.
MARCHAND, F.; PERRETTI, M.; MCMAHON, S. B. Role of the immune system in chronic pain. **Nature Review Neuroscience**, v. 6, n. 7, p. 521-532, 2005.

MARDINI, H. E.; KIP, K. E.; WILSON, J. W. Crohn's disease: a two-year prospective study of the association between psychological distress and disease activity. **Digestive Diseases and Sciences**, v. 49, n. 3, p. 492- 497, 2004.

MARQUES-DEAK, A. H.; NETO, F. L.; DOMINGUEZ, W. V.; SOLIS, A. C.; KURCGANT, D.; SATO, F.; ROSS, J. M.; PRADO, E. B. Cytokine profiles in women with different subtypes of major depressive disorder. **Journal of Psychiatric Research**, v. 41, p. 152–159, 2007.

MARINO, F.; COSENTINO, M.; BOMBELLI, R.; FERRARI, M.; LECCHINI, S.; FRIGO, G. Endogenous catecholamine synthesis, metabolism storage, and uptake in human peripheral blood mononuclear cells. **Experimental Hematology**, v. 27, p. 489- 495, 1999.

MARTELLI, E. A.; TOTH, E.; SEGRE, A. D.; CORSICO, N. Mechanism of inhibition of experimental inflammation by antidepressant drugs. **European Journal of Pharmacology**, v. 2, p. 229- 233, 1967.

MATSUNAGA, K.; KLEIN, T. W.; FRIEDMAN, H.; YAMAMOTO, Y. Involvement of nicotinic acetylcholine receptors in suppression of antimicrobial activity and cytokine responses of alveolar macrophages to Legionella pneumophila infection by nicotine. **Journal of Immunology**, v. 167, n. 11, p. 6518- 6524, 2001.

MAUL, J.; LODDENKEMPER, C.; MUNDT, P.; BERG, E.; GIESE, T.; STALLMACH, A.; ZEITZ, M.; DUCHMANN, R. Peripheral and intestinal regulatory CD4+ CD25 high T cells in inflammatory bowel disease. **Gastroenterology**, v. 128, p. 1868- 1878, 2005.

MAX, M. B.; SCHAFER, S. C.; CULNANE, M.; SMOLLER, B.; DUBNER, R.; GRACELY, R. H. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. **Neurology**, v. 9, p. 1427- 1432, 1988.

MAXWELL, JR.; VINEY, J. L. Overview of mouse models of inflammatory bowel disease and their use in drug discovery. **Current protocols in pharmacology**, v. 47, cap. 5, p. 5. 57.1-5.57.19, 2009.

MAYNARD, C. L.; WEAVER, C. T. Intestinal effector T cells in health and disease. **Immunity**, v. 31, p. 389- 400, 2009.

MAYORGA, A. J.; LUCKI, I. Limitations on the use of the C57BL/6 mouse in the tail suspension test. **Psychopharmacology**, v. 155, p. 110-112, 2001.

MCALINDON, M. E.; HAWKEY, C. J.; MAHIDA, Y. R. Expression of interleukin 1 beta and interleukin 1 beta converting enzyme by intestinal macrophages in health and inflammatory bowel disease. **Gut**, v. 42, p. 214- 219, 1998.

MCCARTY, M. F. Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: down-regulation with essential fatty acids, ethanol and pentoxifylline. **Medicine Hypotheses**, v. 52, p. 465-477, 1999.

McKIM, W. A. **Research design and the behavioral analysis of drug effects**. In: McKIM, W. A. (Ed.) Drugs and behavior: an introduction to behavioral pharmacology. Upper Saddle River, New Jersey: Prentice Hall, 2003, p. 24- 38.

MELGAR, S.; KARLSSON, A.; MICHAËLSSON, E. Acute colitis induced by dextran sulfate sodium progresses to chronicity in C57BL/6 but not in BALB/c mice: correlation between symptoms and inflammation. **American Journal of Physiology:** gastrointestinal and liver physiology, v. 288, p. 1328- 1338, 2005.

MELGAR, S.; BJURSELL, M.; GERDIN, A. K.; SVENSSON, L.; MICHAËLSSON, E.; BOHLOOLY-Y, M. Mice with experimental colitis show an altered metabolism with decreased metabolic rate. **American Journal Physiology Gastrointestinal Liver Physiology**, v. 292, n. 1, p. G165- G172, 2007.

MELGAR, S.; KARLSSON, L.; REHNSTRÖM, E.; KARLSSON, A.; UTKOVIC, H.; JANSSON, L.; MICHAËLSSON, E. Validation of murine dextran sulfate sodium-induced colitis using four therapeutic agents for human inflammatory bowel disease. **International Immunopharmacology**, v. 8, n. 6, p. 836- 844, 2008.

MELMED, G. Y.; TARGAN, S. R. Future biologic targets for IBD: potentials and pitfalls. **Nature Reviews Gastroenterology & Hepatology**, v. 7, n. 2, p. 110- 117, 2010.

MIKOVA, O.; YAKIMOVA, R.; BOSMANS, E.; KENIS, G.; MAES, M. Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. **European Neuropsychopharmacology**, v. 11, p. 203- 208, 2001.

MIKOCKA-WALUS, A. A.; TURNBULL, D. A.; MOULDING, N. T.; WILSON, I. G.; ANDREWS, J. M.; HOLTMANN, G. J. Antidepressants and inflammatory bowel disease: a systematic review. **Clinical Practice and Epidemiology in Mental Health**, v. 2, n. 24, p. 1- 9, 2006.

MIKOCKA-WALUS**,** A. A.; BENJAMIN A. L.; STEWART, J.; ANDREWS, J. A magic pill? A qualitative analysis of patients' views on the role of antidepressant therapy in inflammatory bowel disease (IBD). **Gastroenterology,** v. 12, n. 93, p. 2- 9, 2012.

MILLER, A. H.; LACKNER, C. Tricyclic antidepressants and immunity. In: MILLER, A. H. (Ed.). **Depressive disorders and immunity**. Washington (DC): American Psychiatry Press**,** 1989. p. 85-104.

MITTERMAIER, C.; DEJACO, C.; WALDHOER, T.; OEFFERLBAUER-ERNST, A.; MIEHSLER, W.; BEIER, M.; TILLINGER, W.; GANGL, A.; MOSER, G. Impact of

depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. **Psychosomatic Medicine**, v. 66, n. 1, p. 79–84, 2004.

MIYATA, S.; HIRANO, S.; KAMEI, J. Diabetes attenuates the antidepressant-like effect mediated by the activation of 5-HT(1A) receptor in the mouse tail suspension test. **Neuropsychopharmacology**, v. 29, n. 3, p. 461- 469, 2003.

MONANE, M.; AVORN, J.; BEERS, M. H.; EVERITT, D. E. Anticholinergic drug use and bowel function in nursing home patients. **Archives of Internal Medicine**, v. 153, n. 5, p. 633-638, 1993.

MORGAN, M. E.; ZHENG, B.; KOELINK, P. J.; VAN DE KANT, H. J.; HAAZEN, L. C.; VAN ROEST, M.; GARSSEN, J.; FOLKERTS, G.; KRANEVELD, A. D. New perspective on Dextran sodium sulfate colitis: antigen-specific T cell development during intestinal inflammation. **PLoS One**, v. 8, n. 7, p. 1- 12, 2013.

MUDTER, J.; WIRTZ, S.; GALLE, P. R.; NEURATH, M. F. A new model of chronic colitis in SCID mice induced by adoptive transfer of CD62L CD4 T cells: insights into the regulatory role of interleukin-6 on apoptosis. **Pathobiology**, v. 70, p. 170- 176, 2002.

MUDTER, J.; NEURATH, M. F. Il-6 Signaling in inflammatory bowel disease: pathophysiological role and clinical relevance. **Inflammatory Bowel Disease**, v. 13, n. 8, p. 1016- 1023, 2007.

MURTHY, S. N.; COOPER, H. S.; SHIM, H.; SHAH, R. S.; IBRAHIM, S. A.; SEDERGRAN, D. J. Treatment of dextran sulfate sodium-induced murine colitis by intracolonic cyclosporine. **Digestive diseases and sciences**, v. 37, p. 1722-1734, 1993.

NAITO, Y.; TAKAGI, T.; HANDA, O.; ISHIKAWA, T.; NAKAGAWA, S.; YAMAGUCHI, T.; YOSHIDA, N.; MINAMI, M.; KITA, M.; IMANISHI, J.; YOSHIKAWA, T. Enhanced intestinal inflammation induced by dextran sulfate sodium in tumor necrosis factor-alpha deficient mice. **Journal Gastroenterology Hepatology**, v. 18, n. 5, p. 560- 569, 2003.

NAITO, Y.; TAKAGI, T.; UCHIYAMA. K. KURODA, M.; KOKURA, S.; ICHIKAWA, H.; YANAGISAWA, R.; INOUE, K.; TAKANO, H.; SATOH, M.; YOSHIDA, N.; OKANOUE, T.; YOSHIKAWA, T. Reduced intestinal inflammation induced by dextran sodium sulfate in interleukin-6-deficient mice. **International Journal of Molecular Medicine**, v. 14, p.191-196, 2004.

NAITO Y.; TAKAGI, T.; YOSHIKAWA, T. Neutrophil-dependent oxidative. **Clinic Biochememical Nutrition**, v. 41, n. 1, p. 18–26, 2007.

NALEPA, I. The effect of psychotropic drugs on the interaction of protein kinase C with second messenger system in the rat cerebral cortex. **Polish Journal of Pharmacology**, v. 46, p. 1-14, 1994.

NASYROVA, R. F.; SOTNIKOVA, L. S.; BAYSTRUKOVA, N. V.; KRIVOSCHCHEKOVA, G. V.; NOVITSKY, V. V.; KUPRIYANOVA, I. E.; SEMKE, V. Y.; NASLEDNIKOVA, I. O.; BAYKOV, A. N. Psychoimmune interactions in women of

reproductive age with endometriosis. **Bull Experimental Medicine and Biology**, v. 152, n. 1, p. 93-97, 2011.

NELSON, J. C. A review of the efficacy of serotonergic and noradrenergic reuptake inhibitors for treatment of major depression. **Biological Psychiatry**, v. 46, p. 1301- 1308, 1999.

NG, S. C.; BERNSTEIN, C. N.; VATN, M. H.; LAKATOS, P. L.; LOFTUS, E. V. JR.; TYSK, C.; O'MORAIN, C.; MOUM, B.; COLOMBEL, J. F. Geographical variability and environmental risk factors in inflammatory bowel disease. **Gut**, v. 62, n. 4; p. 630- 649, 2013.

NI, J.; CHEN, S-F.; HOLLANDER, D. Effects of dextran sulphate sodium on intestinal epithelial cells and intestinal lymphocytes, **Gut**, v. 39, p. 234- 241, 1996.

O'BRIEN, S. M.; SCOTT, L. V.; DINAN, T. G. Cytokines: abnormalities in major depression and implications for pharmacological treatment. **Human Psychopharmacology**, v. 19, p. 397-403, 2004.

OBUCHOWICZ, E.; KOWALSKI, J.; LABUZEK, K.; KRYSIAK, R.; PENDZICH, J.; HERMAN, Z. S. Amitriptyline and nortriptyline inhibit interleukin-1 release by rat mixed glial and microglial cell cultures. **International Journal Neuropsychopharmacol**, v. 9, n. 1, p. 27- 35, 2006.

O'CONNOR, J. C.; JOHNSON, D. R.; FREUND, G. G. Psychoneuroimmune implications of type 2 diabetes: redux. **Immunology and Allergy Clinics of North America**, v. 29, n. 2, p. 339-58, 2009.

O'SHEA, J. J.; MURRAY, P. J. Cytokine signaling modules in inflammatory responses. **Immunity**, v. 28, p. 477- 487, 2008.

OH, S. Y.; CHO, K. A.; KANG, J. L.; KIM, K. H.; WOO, S. Y. Comparison of experimental mouse models of inflammatory bowel disease. **International Journal Molecular Medicine**, v. 33, n. 2, p. 333- 340, 2014.

OHKUSA, T. Production of experimental ulcerativecolitis in hamsters by dextran sulfate sodiumand change in intestinal microflora (in Japanese). **Japan Journal of Gastroenteroly**, v. 82, p. 1327- 1336, 1985.

OHKUSA, T.; OKAYASU, I.; TOKOI, S.; ARAKI, A.; OZAKI, Y. Changes in bacterial phagocytosis of macrophages in experimental ulcerative colitis. **Digestion**, v. 56, n. 2, p. 159-164, 1995.

OKADA, Y.; TSUZUKI, Y.; MIYAZAKI, J.; MATSUZAKI, K.; HOKARI, R.; KOMOTO, S.; KATO, S.; KAWAGUCHI, A.; NAGAO, S.; ITOH, K.; WATANABE, T.; MIURA, S. Propionibacterium freudenreichii component 1.4-dihydroxy-2-naphthoic acid (dhna) attenuates dextran sodium sulphate induced colitis by modulation of bacterial flora and lymphocyte homing. **Gut**, v. 55, n. 5, p. 681- 688, 2006.

OKAYASU, I.; HATAKEYAMA, S.; YAMADA, M.; OHKUSA, T.; INAGAKI, Y.; NAKAYA, R. A novel method in the induction of reliable experimental acute and chronic

ulcerative colitis in mice. **Gastroenterology**, v. 98, n. 3, p. 694-702, 1990.

ONALI, P.; DEDONI, S.; OLIANAS, M. C. Direct agonist activity of tricyclic antidepressants at distinct opioid receptor subtypes. **Journal of Pharmacology Experimental Therapeutic**s, v. 332, n. 1, p. 255- 265, 2010.

OXENKRUG, G. F. Genetic and hormonal regulation of tryptophan kynurenine metabolism: implications for vascular cognitive impairment, major depressive disorder, and aging. **Annais New York Academic Science**, v. 1122, p. 35- 49, 2007.

OVADIA, H.; LUBETZKI-KORN, I.; ABRAMSKY, O. Dopamine receptors on isolated membranes of rat thymocytes. **Annais of New York Academy of Science**, v. 496, p. 211-216, 1987.

PACE, T. W.; HU, F.; MILLER, A. H. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. **Brain Behavior Immunology**, v. 21, p. 9- 19, 2007.

PANKAJ, S.; SANTOSH, K. S.; RAJMANI, P. New approach for the determination of tricyclic antidepressant amitriptyline using β-cyclodextrin-peg system via spectrophotomerty. **Journal of Analytical Sciences, Methods and Instrumentation**, v. 2, n. 2, p. 103- 107, 2012.

PALANZA, P. Animal models of anxiety and depression: how are females different? **Neuroscience & Biobehavioral Reviews**, v. 25, p. 219–233, 2001.

PALERMO-NETO, J.; MASSOCO, C. O.; SOUZA, R. W. Effects of physical and psychological stressors on behavior, macrophage activity, and Ehrlich tumor growth. **Brain Behavior Immunology**, v. 17, n. 1, p. 43-54, 2003.

PAPADAKIS, K. A.; TARGAN, S. R. Role of cytokines in the pathogenesis of inflammatory bowel disease. **Annual Review Medicine**, v. 51, p. 289–298, 2000.

PERSE, M.; CERAR, A. Dextran sodium sulphate colitis mouse model: traps and tricks. **Journal of Biomedicine and Biotechnology**, v. 2012, p. 1- 13, 2012.

PITHADIA, A. B.; JAIN, S. Treatment of inflammatory bowel disease (IBD). **Pharmacological Reports**, v. 63, p. 629- 642, 2011.

PLEVY, S. E.; LANDERS, C. J.; PREHN, J.; CARRAMANZANA, N. M.; DEEM, R. L.; SHEALY, D.; TARGAN, S. R. A role for TNF-alpha and mucosal T helper-1 cytokines in the pathogenesis of Crohn's disease. **Journal of Immunology**, v. 159; p. 6276- 6282, 1997.

PODOLSKY, D. K. Inflammatory bowel disease. **New England Journal of Medicine**, v. 347, p. 417–429, 2002.

PORITZ, L. S.; GARVER, K. I.; GREEN, C.; FITZPATRICK, L.; RUGGIERO, F.; KOLTUN, W. A. Loss of the tight junction protein ZO-1 in dextran sulfate sodium induced colitis. **Journal of Surgical Research**, v. 140, n. 1, p. 12-19, 2007.

PORSOLT, R. D., Animal models of depression: utility for transgenic research. **Review Neuroscience**, v. 11, p. 53- 58, 2000.

PORTELA, C. P.; MASSOCO, C. O.; DE LIMA W. T.; PALERMO-NETO, J. Stress-induced increment on total bronchoalveolar cell count in ova-sensitized rats. **Physiology Behavior**, v. 72, p. 415- 420, 2001.

PRADO, P. S. A.; SOARES, M. F.; LIMA, F.O.; SCHOR,N.; TEIXEIRA, V. P. Amitriptyline aggravates the fibrosis process in a rat model of infravesical obstruction. **International Journal of Experimental Pathology**, v. 93, n. 3, p. 218- 224, 2012.

PRAVDA, J. Radical Induction Theory of ulcerative colitis. **World Journal of Gastroenterology**, v. 11, p. 2371- 2384, 2005.

PUCAK, M. L.; KAPLIN, A. I. Unkind cytokines: current evidence for the potential role of cytokines in immune-mediated depression. **International Review Psychiatry**, v. 17, p. 477-483, 2005.

QUARTERO, A.; MEINECHE-SCHMIDT, V.; MURIS, J.; RUBIN, G.; DE WIT, N. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. **Cochrane Database of Systematic Reviews**, n. 2, p. 1- 120, 2005.

QUILICI, F.A. **Retocolite Ulcerativa**. São Paulo: Lemos editorial, 2002, p. 5- 95.

RACHMILEWITZ, D.; SIMON, P. L.; SCHWARTZ, L. W. Inflammatory mediators of experimental colitis in rats. **Gastroenterology**, v. 97, n. 2, p. 326- 337, 1989.

RAHIMI, R. Efficacy of tricyclic antidepressants in irritable bowel syndrome: a meta-analysis. **World Journal of Gastroenterology**, v. 15, n. 13, p. 1548, 2009.

RAHIMI, H. R.; SHIRI, M.; RAZMI, A. Antidepressants can treat inflammatory bowel disease through regulation of the nuclear factor-kappab/nitric oxide pathway and inhibition of cytokine production: a hypothesis. **World Journal of Gastrointestinal Pharmacology and Therapeutics**, v. 3, n. 6, p. 83- 85, 2012.

RAJAGOPALAN, M.; KURIAN, G.; JOHN, J. Symptom relief with amitriptyline in the irritable bowel syndrome. **Journal Gastroenterology Hepatology**, v. 13, n. 7, p. 738- 741, 1998.

RAMPTON, D. Management of difficult inflammatory bowel disease: where are we now? **World Journal of Gastroenterology**, v. 6, n. 3, p. 315- 323, 2000.

RANG, H. P.; DALE, M. M.; RITTER, J. M. **Farmacologia**. 3. ed. Rio de Janeiro: Guanabara Koogan, 1997. 692 p.

REN, K.; DUBNER, R. Interactions between the immune and nervous systems in pain. **Nature Medicine**, v. 16, p. 1267-1276, 2010.

RETTORI, V. Neuroimmune interactions. **Experimental Physiology**, v. 92, n. 5, p. 799-800, 2007.

RIBEIRO, A.; ALMEIDA, V.; COSTOLA-DE-SOUZA, C.; FERRAZ-DE-PAULA, V.; PINHEIRO, M. L.; , VITORETTI, L. B.; GIMENES-JUNIOR, J. A.; AKAMINE, A. T.; CRIPPA, J. A.; TAVARES-DE-LIMA, W.; PALERMO-NETO, J. Cannabidiol improves lung function and inflammation in mice submitted to LPS- induced acute lung injury. **Immunopharmacology Immunotoxicoogy**, v. 37, n. 1, p. 35- 41, 2015.

RICKETTS, C. R. Dextran sulphate-a synthetic analogue of heparin. **Biochemical**, v. 51, n. 1, p. 129- 33, 1952.

ROITT, I.; BROSTOFF, J.; MALE, D. **Immunology**. London: Mosby, 1996, v. 4, p. 420.

ROSENFELD, G. Corante pancrômico para hematologia e citologia clínica. Nova combinação dos componentes de May-Grunwald e do Giemsa num só corante de emprego rápido. **Memórias do Instituto Butantan**, v. 20, p. 329-335, 1947.

ROTHWELL, N. J.; HOPKINS, S. J. Cytokines and the nervous system: actions and mechanisms. **Trends Neuroscience**, v. 18, p. 130-136, 1995.

RUGTVEIT, J.; HARALDSEN, G.; HØGÅSEN, A. K.; BAKKA, A.; BRANDTZAEG, P.; SCOTT, H. Respiratory burst of intestinal macrophages ininflammatory bowel disease is mainly caused by CD14+L1+ monocyte derived cells. **Gut**, v. 37, p. 367- 373, 1995.

_____. et al. Cytokine profiles differ in newly recruited and resident subsets of mucosal macrophages from inflammatory bowel disease. **Gastroenterology**, v. 112, p. 1493-1505, 1997.

RUSSO, S.; KEMA, I. P.; BOSKER, F.; HAAVIK, J.; KORF, J. Tryptophan as an evolutionarily conserved signal to brain serotonin: molecular evidence and psychiatric implications. **World Journal Biology Psychiatry**, v. 13, p. 1- 11, 2007.

SACERDOTE, P.; BIANCHI, M.; PANERAI, A. E. In vivo and in vitro clomipramine treatment decreases the migration of macrophages in the rat. **European Journal of Pharmacology**, v. 319, p. 287- 290, 1997.

SADEGHI, H.; HAJHASHEMI, V.; MINAIYAN, M.; MOVAHEDIAN, A.; TALEBI, A. A study on the mechanisms involving the anti-inflammatory effect of amitriptyline in carrageenan-induced paw edema in rats. **European Journal of Pharmacology**, v. 30, n. 667, p. 396-401, 2011.

SAILOR, R. B. Pathogenesis and immune mechanisms of chronic inflammatory bowel diseases. **American Journal of Gastroenterology**, v. 92, p. 5S- 11S, 1997. Suplement, 12.

SAKAI, M.; FERRAZ-DE-PAULA, V.; PINHEIRO, M. L.; RIBEIRO, A.; QUINTEIRO-FILHO, W. M; RONE, M. B.; MARTINEZ-ARGUELLES, D. B.; DAGLI, M. L.; PAPADOPOULOS, V.; PALERMO-NETO, J. Translocator protein (18 kDa) mediates the pro-growth effects of diazepam on Ehrlich tumor cells in vivo. **European Journal of Pharmacology**, v. 626, n. 2-3, p. 131-138, 2010.

SANDERS, V. M. Interdisciplinary research: noradrenergic regulation of adaptive immunity. **Brain Behavior Immunology**, v. 20, n. 1, p. 1-8, 2006.

SANDERS, R. D.; HUSSELL, T.; MAZE, M. Sedation & immunomodulation**. Critical Care Clinic**, v. 25, p. 3, p. 551-570, 2009.

SANKARAN-WALTERS, S.; MACAL, M.; GRISHINA, I.; NAGY, L.; GOULART, L.; COOLIDGE, K.; LI, J.; FENTON, A.; WILLIAMS, T.; MILLER, M. K.; FLAMM, J.; PRINDIVILLE, T.; GEORGE, M.; DANDEKAR, S. Sex differences matter in the gut: effect on mucosal immune activation and inflammation. **Biology of Sex Differences**, v. 4, n. 1, p. 10, 2013.

SALEH, M.; TRINCHIERI, G. Innate immune mechanisms of colitis and colitis-associated colorectal cancer. **Nature Reviews Immunology**, v. 11, n. 1, p. 9-20, 2011.

SALICRÚ, A. N.; SAMS, C, F.; MARSHALL, G. D. Cooperative effects of corticosteroids and catecholamines upon immune deviation of the type-1/type-2 cytokine balance in favor of type-2 expression in human peripheral blood mononuclear cells. **Brain Behavior Immunology**, v. 21, n. 7, p. 913- 920, 2007.

SARTOR, R. B. Mechanisms of Disease: Pathogenesis of Crohn's Disease and Ulcerative Colitis. Nature clinical practice. **Gastroenterology & hepatology**, v. 3, n. 7, p. 390- 407, 2006.

_____. Microbial influences in inflammatory bowel diseases. **Gastroenterology**, v. 134, n. 2, p. 577- 94, 2008.

SATSANGI, J.; WOLSTENCROFT, R. A.; CASON, J.; AINLEY, C. C.; DUMONDE, C. C; THOMPSON, R. P. H. Interleukin 1 in Crohn's disease. **Clinical and Experimental Immunology**, v. 67, p. 594- 605, 1987.

SATSANGI, J.; VERMEIRE, S.; PARKES, M.; PEETERS, M.; VYAS, P.; RUTGEERTS, P.; JEWELL, D. Genetics of inflammatory bowel disease. **Clinical science**, v. 94, v. 5, p. 473-478, 1998.

SA- ROCHA, V. M.; SA-ROCHA, L. C.; PALERMO-NETO, J. Variations in behavior, innate immunity and host resistance to B16F10 melanoma growth in mice that present social stable hierarchical ranks. **Physiology Behavior**, v. 88, n. 1-2, p. 108-115, 2006.

SCHLATTER, J.; ORTUÑO, F.; CERVERA-ENGUIX, S. Lymphocyte subsets and lymphokine production in patients with melancholic versus nonmelancholic depression. **Psychiatry Research**, v. 128, n. 3, p. 259-265, 2004.

SCHINDLER, W.; HÄFLIGER, F. Derivate desiminodibenzyl. **Helvetica Chimica Acta**, v. 37, p. 427,1954.

SCHOEB, T. R.; BULLARD, D. C. Microbial and histopathologic considerations in the use of mouse models of inflammatory bowel diseases. **Inflammatory Bowel Disease**, v. 18, p. 1558-1565, 2012.

SCHOULTZ, M.; ATHERTON, I.; HUBBARD, G.; WATSON, A. J. Assessment of causal link between psychological factors and symptom exacerbation in inflammatory bowel disease: a protocol for systematic review of prospective cohort studies. **Systematic Reviews**, v. 2, p. 2- 8, 2013.

SCHROEDER, K.W.; TREMAINE, W. J.; ILSTRUP, D. M. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. **New England Journal of Medicine**, v. 317, p.1625–1629, 1987.

SCHUH, J. C. L.; VINEY, J. L. Endogenous bacterial flora modulate experimentally-induced colitis in mice. **Veterinary Pathology**, v. 33, p.1-12, 1996.
SELYE, H. What is stress? **Metabolism**, v. 5, p. 525-530, 1956.

SHA, T.; IGAKI, K.; YAMASAKI, M.; WATANABE, T.; TSUCHIMORI, N. Establishment and Validation of a New Semi-Chronic Dextran Sulfate Sodium-Induced Model of Colitis in Mice. International **Immunopharmacology**, v. 15, n. 1, p. 23- 9, 2013.

SHEN, Y.; CONNOR, T. J.; NOLAN, Y.; KELLY, J. P.; LEONARD, B. E. Differential effect of chronic antidepressant treatment on lypopolysaccharide-induced depressive like behavioural symptoms in the rat. **Life Science**, v. 65, p. 1773- 1786, 1999.

SHERMAN, A. D.; ALLERS, G. L.; PETTY, F.; HENN, F. A. A neuropharmacologically-relevant animal model of depression. **Neuropharmacology**, v. 18, p. 891- 893, 1979.

SILVA, P. **Farmacologia**, 5. ed. Rio de Janeiro, Guanabara Koogan, 1998, cap. 32.

SILVEIRA, G.; TARLEY, R. T. Determinação turbidimétrica do antidepressivo amitriptilina em sistema fia explorando a formação do par iônico com lauril sulfato de sódio. **Quimica Nova**, v. 31, n. 7, p. 1653-1659, 2008.

SIMMONS, D. L.; TAN, S.; TENEN, D. G.; NICHOLSON-WELLER, A.; SEED, B. Monocyte antigen CD14 is a phospholipid anchored membrane protein. **Blood**, v. 73, p. 284-289, 1989.

SMITH, R. S. The macrophage theory of depression. **Medicine Hypotheses**, v. 35, n. 4, p. 298-306, 1991.

SOLOMON, L.; MANSOR, S.; MALLON, P.; DONNELLY, E.; HOPER, M.; LOUGHREY, M.; KIRK, S.; GARDINER, K. The dextran sulphate sodium (DSS) model of colitis: an overview. **Comparative Clinical Pathology**, v. 19, n. 3, p. 235- 239, 2010.

SONG, C.; LEONARD B. E. **Fundamentals of psychoneuroimmunology**. Chichester, U.K.: Wiley, J. and Sons, 2000.

SOUBA, W. W. Cytokine control of nutrition and metabolism during critical illness. **Current Problems in Surgery**, v. 31, p. 577- 643, 1994.

SPENCER, A. U.; YANG, H.; HAXHIJA, E. Q.; WILDHABER, B. E.; GREENSON, J. K.; TEITELBAUM, D. H. Reduced severity of a mouse colitis model with angiotensin converting enzyme inhibition. **Digestive Disease Science**, v. 52, p. 1060-1070, 2007.

STAHL, S. M. **Psychopharmacology of antidepressants**. London: Martin Dunitz, 1997. 114 p.

_____. Basic psychopharmacology of antidepressants. Part 1. Antidepressants have seven distinct mechanisms of action. **Journal Clinic Psychiatry**, v. 59, p. 5- 14, 1998.

_____. **Psicofarmacologia:** base neurocientífica e aplicações práticas. 2. ed. Rio de Janeiro: Médica e Científica, 2002. p. 359- 445.

STÅHLBERG, D.; VERESS, B.; MÅRE, K.; GRANQVIST, S.; AGREN, B.; RICHTER, S.; LÖFBERG, R. Leucocyte migration in acute chronic inflammatory bowel disease: comparison of histological assessment and TC-99m-HMPAO labeled leucocyte scan. **American Journal of Gastroenteroly**, v. 92, p. 283–288, 1997.

STANKEVICIUS, D.; RODRIGUES-COSTA, E. C.; CAMILO FLÓRIO, J.; PALERMO-NETO, J. Neuroendocrine, behavioral and macrophage activity changes induced by picrotoxin effects in mice. **Neuropharmacology**, v. 54, n. 2, p. 300-308, 2008.

STERU, L.; CHERMAT, R.; THIERRY, B.; SIMON, P. The tail suspension test: a new method for screening antidepressants in mice. **Psychopharmacology**, v. 85, n. 3, p. 367-370, 1985.

STEVCEVA, L.; PAVLI, P.; HUSBAND, A. J.; DOE, W. F. The inflammatory infiltrate in the acute stage of the dextran sulphate sodium induced colitis: B cell response differs depending on the percentage of dss used to induce it. **Biomed Central Clinical Pathology**, v. 1, n. 1, p. 3, 2001.

STODDARD, S. L.; BERGDALL, V. K.; TOWNSEND, D. W.; LEVIN, B. E. Plasma catecholamines associated with hypothalamically-elicited defense behavior. **Physiology Behavior**, v. 36, n. 5, p. 867-873, 1986.

STROBER, W.; FUSS, I. J.; BLUMBERG, R. S. The immunology of mucosal models of inflammation. **Annual Review of Immunology**, v. 20, p. 495- 549, 2002.

STROBER, W.; FUSS, I. J. Proinflammatory cytokines in the pathogenesis of inflammatory bowel diseases. **Gastroenterology**, v. 140, p. 1756- 1767, 2011.

STURM, A.; DE SOUZA, H. S; FIOCCHI, C. Mucosal T cell proliferation and apoptosis in inflammatory bowel disease. **Current Drug Targets**, v. 9, p. 381-387, 2008.

SUNDBERG, J. P.; ELSON, C.O.; BEDIGIAN, H.; BIRKENMEIER, E. H. Spontaneous, heritable colitis in a new substrain of C3H/HeJ mice. **Gastroenterology**, v. 107, n. 6, p. 1726-1735, 1994.

SUSSMAN, N.; STAHL, S. Update in the pharmacotherapy of depression. **American Journal of Medicine**, v. 101, n. 6A, p. 265-365, 1996.

SUTCIGIL, L.; OKTENLI, C.; MUSABAK, U.; BOZKURT, A.; CANSEVER, A.; UZUN, O.; SANISOGLU, S. Y.; YESILOVA, Z.; OZMENLER, N.; OZSAHIN, A.; SENGUL, A. Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy. **Clinical and Developmental Immunology**, v. 2007, p. 1- 6, 2007.

SZUSTER-CIESIELSKA, A.; TUSTANOWSKA-STACHURA, A.; SLOTWINSKA, M; MARMUROWSKA-MICHAŁOWSKA, H.; KANDEFER-SZERSZEŃ, M. In vitro immunoregulatory effects of antidepressants in healthy volunteers. **Polish journal of pharmacology**, v. 55, n. 3, p. 353- 362, 2003.
TAI, Y. H.; WANG, Y. H.; WANG, J. J.; TAO, P. L.; TUNG, C. S.; WONG, C. S. Amitriptyline suppresses neuroinflammation and up-regulates glutamate transporters in morphine-tolerant rats. **Pain**, v. 124, n. 1-2, p. 77- 86, 2006.

TAKAHASHI, M.; NAKAMURA, K.; HONDA, K.; KITAMURA, Y.; MIZUTANI, T.; ARAKI, Y.; KABEMURA, T.; CHIJIIWA, Y.; HARADA, N.; NAWATA, H. An inverse correlation of human peripheral blood regulatory T cell frequency with the disease activity of ulcerative colitis. **Digestive Diseases and Sciences**, v. 51, n. 4, p. 677- 686, 2006.

TALER, M.; GIL-AD, I.; LOMNITSKI, L.; KOROV, I.; BAHARAV, E.; BAR, M.; ZOLOKOV, A.; WEIZMAN, A. Immunomodulatory effect of selective serotonin reuptake inhibitors (SSRIs) on human T lymphocyte function and gene expression. **European Neuropsychopharmacology**, v. 17, p. 774- 780, 2007.

TAYEBATI, S. K.; BRONZETTI, E.; MORRA DI CELLA, S.; MULATERO, P.; RICCI, A.; ROSSODIVITA, I.; SCHENA, M.; SCHIAVONE, D.; VEGLIO, F.; AMENTA, F. In situ hybridization and immunocytochemistry of alpha- adrenoceptors in human peripheral blood lymphocytes. **Journal of Autonomic Pharmacology**, v. 20, p. 305-312, 2000.

THAKORE, J. H.; DINAN, T. G. Effect of fluoxetine on dexamethasone-induced growth hormone release in depression: a double-blind, placebo-controlled study. **American Journal Psychiatry**, v. 152, p. 616- 618, 1995.

THIELE, J.; HOLZINGER, O. Properties of o-diaminodibenzyl. **Liebigs Annalen der Chemie**, v. 305, p. 96-102, 1899.

TOLEDO, R. A.; MAZO, L. H.; SANTOS, M. C.; HONÓRIO, K. M.; DA SILVA, A. B. F.; CAVALHEIRO, E. T. G. Estudo eletroquímico e químico-quântico da oxidação do antidepressivo tricíclico amitriptilina. **Química Nova**, v. 28, n. 3, p. 456-461, São Paulo, 2005.

TORRENTE, C. E.; VÁZQUEZ, D. E.; GAY, E. C. Use of amitriptyline for the treatment of chronic tension- type headache. **Medicina Oral Patologia Oral y Cirugia Bucal**, v. 13, n. 9, p. E567-572, 2008.

TRACEY, K. J. Tumor necrosis factor: a pleiotrophic cytokine and therapeutic target. **Annual Review of Medicine**, v. 45, p. 491–503, 1994.

TSAO, C. W., LIN, Y. S., CHEN, C. C., BAI, C. H., WU, S. R. Cytokines and serotonin transporter in patients with major depression. **Program Neuropsychopharmacology Biology Psychiatry**, v. 30, p. 899- 905, 2006.

TSUKADA, Y.; NAKAMURA, T.; IIMURA, M.; IIZUKA, B.E.; HAYASHI, N. Cytokine profile in colonic mucosa of ulcerative colitis correlates with disease activity and response to granulocytapheresis. **American Journal of Gastroenterology**, v. 97, p. 820–2828, 2002.

TUGLU, C.; KARA, S. H.; CALIYURT, O.; VARDAR, E.; ABAY, E. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. **Psychopharmacology**, v. 170, p. 429- 433, 2003.

UMEHARA, Y.; KUDO, M.; NAKAOKA, R.; KAWASAKI, T.; SHIOMI, M. Serum proinflammatory cytokines and adhesion molecules in ulcerative colitis. **Hepatogastroenterology**, v. 53, p. 879-882, 2006.

VALATAS, V.; VAKAS, M.; KOLIOS, G. The value of experimental models of colitis in predicting efficacy of biological therapies for inflammatory bowel diseases. **American Journal of Physiology- Gastrointestinal and Liver Physiology**, v. 305, p. G763–G785, 2013.

VAN DER HEYDEN, J. A.; MOLEWIJK, E.; OLIVIER, B. Strain differences in response to drugs in the tail suspension test for antidepressant activity. **Psychopharmacology**, v. 92, p. 127- 130, 1987.

VAN DER WORP, H. B.; HOWELLS, D. W.; SENA, E. S.; PORRITT, M. J.; REWELL, S.; O'COLLINS, V.; MACLEOD, M. R. Can animal models of disease reliably inform human studies? **PLoS Medicine**, v. 7, p. 1-8, 2010. e1000245.

VAN DOP, W. A.; MARENGO, I.; TE VELDE, A. A.; CIRAOLO, E.; FRANCO, I.; TEN KATE, F. J.; BOECKXSTAENS, G. E.,C.; HOMMES, D. W.; HIRSCH, E.; VAN DEN BRINK, G. R. The absence of functional PI3Kgamma prevents leukocyte recruitment and ameliorates DSS-induced colitis in mice. **Immunology Letters**, v. 131, p. 33-39, 2010.

VARGHESE, A. K.; VERDÚ, E. F.; BERCIK, P.; KHAN, W. I.; BLENNERHASSETT, P. A.; SZECHTMAN, H.; COLLINS, S. M. Antidepressants attenuate increased susceptibility to colitis in a murine model of depression. **Gastroenterology**, v. 130, n. 6, p. 1743- 1753, 2006.

VAUGEOIS, J. M.; ODIEVRE, C.; LOISEL, L.; COSTENTIN, J. A genetic mouse model of helplessness sensitive to imipramine. **European Journal of Pharmacology**, v. 316, p. R1–R2, 1996.

VENKATESHA, S. H.; DUDICS, S.; ACHARYA, B.; MOUDGIL, K. D. Cytokine-modulating strategies and newer cytokine targets for arthritis therapy. **International Journal of Molecular Sciences**, v. 16, n. 1, p. 887- 906, 2015.

VENKATRAMAN, A.; RAMAKRISHNA, B. S.; PULIMOOD, A. B.; PATRA, S.; MURTHY, S. Increased permeability in dextran sulphate colitis in rats: time course of development and effect of butyrate. **Scandinavian Journal Gastroenterology**, v. 35, p. 1053- 1059, 2000.

VISMARI, L.; ALVES, G. J.; PALERMO-NETO, J. Depressão, antidepressivos e sistema imune: um novo olhar sobre um velho problema. **Revista Psiquiátrica Clínica**, v. 35, n. 5, p. 196- 204, 2008.

_____. Amitriptyline and acute inflammation: a study using intravitalmicroscopy and the carrageenan- induced paw edema model. **Pharmacology**, v. 86, n. 4, p. 231- 239, 2010.

_____. A possible role to nitric oxide in the anti-inflammatory effects of amitriptyline. Immunopharmacology Immunotoxicology, v. 34, n. 4, p. 578- 585, 2012.

WATSON, C. P.; VERNICH, L.; CHIPMAN, M.; REED, K. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. **Neurology**, v. 51, p. 1166-1171, 1998.

WELDON, M. J.; MASOOMI, A. M.; BRITTEN, A. J.; GANE, J.; FINLAYSON, C. J.; JOSEPH, A. E.; MAXWELL, J. D. Quantification of inflammatory bowel disease activity using technetium-99m HMPAO labeled leucocyte single photon emission computerized tomography (SPECT). **Gut**, v. 3, p. 243–50, 1995.

WILKS S. Morbid appearances in the intestine of Miss Bankes. **London Medical Gazette**, v. 2, p. 264, 1859.

WINTHER, K. V.; JESS, T.; LANGHOLZ, E.; MUNKHOLM, P.; BINDER, V. Survival and cause-specific mortality in ulcerative colitis: follow-up of a population-based cohort in Copenhagen county. **Gastroenterology**, v. 125, p. 1576–1582, 2003.

WITTIG, B.; SEITER, S.; SCHMIDT, D. S.; ZUBER, M.; NEURATH, M.; ZOLLER, M. CD44 variant isoforms on blood leukocytes in chronic inflammatory bowel disease and other systemic autoimmune diseases. **Laboratory Investigation**, v. 79, p. 747- 59, 1999.

WRIGHT, S. D.; RAMOS, R. A.; HERMANOWSKI-VOSATKA, A.; ROCKWELL, P.; DETMERS, P. A. Activation of adhesive capacity of (QR3 on neutrophils by endotoxin: dependence on lipopolysaccharide binding protein and CD14. **Journal of Experimental Medicine**, v. 173, p. 1281- 1286, 1991.

WRONA, D. Neural-immune interactions: an integrative view of the bidirectional relationship between the brain and immune systems. **Journal of Neuroimmunology**, v. 172, n. 1-2, p. 38-58, 2006.

XAVIER, R. J.; PODOLSKY, D. K. Unravelling the pathogenesis of inflammatory bowel

disease. **Nature**, v. 448, n. 7152, p. 427- 434, 2007.

YAMADA, Z.; DEPIERRE, J.; NASSBERGER, L. Tricyclic antidepressants inhibit IL–6, IL–1b, and TNF–a release in human blood monocytes and IL–2 and interferon–gamma in T cells. **Immunopharmacology**, v. 34, p. 27- 37, 1996.

YAMADA, M.; OHKUSA, T.; OKAYASU, I. Occurrence of dysplasia and adenocarcinoma after experimental chronic ulcerative colitis in hamsters induced by dextran sulphate sodium. **Gut,** v. 33, p. 1521- 1527, 1992.

YAMANO, M.; YUKI, H.; YASUDA, S.; MIYATA, K. Corticotropin releasing hormone receptors mediate consensus interferon-alpha YM643-induced depression-like behavior in mice. **Journal of pharmacology and experimental therapeutics**, v. 292, p. 181- 187, 2000.

YAN, Y.; KOLACHALA, V.; DALMASSO, G.; NGUYEN, H.; Laroui, H.; Sitaraman, S. V.; Merlin, D. Temporal and spatial analysis of clinical and molecular parameters in dextran sodium sulfate induced colitis. **PLoS One**, v. 4, n. 6, p. 1-8, 2009.

YARON, I.; SHIRAZI, I.; JUDOVICH, R.; LEVARTOVSKY, D.; CASPI, D.; YARON, M. Fluoxetine and amitriptyline inhibit nitric oxide, prostaglandin E2, and hyaluronic acid production in human synovial cells and synovial tissue cultures. **Arthritis Rheumatology**, v. 42, p. 2561- 2568, 1999.

YOSHIMURA, R., HORI, H., IKENOUCHI-SUGITA, A., UMENE-NAKANO, W., UEDA, N., NAKAMURA, J. Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. **Program Neuropsychopharmacology Biology Psychiatry**, v. 33, p. 722-726, 2009.

YOUNGMAN, K. R.; SIMON, P. L.; WEST, G. A.; COMINELLI, F.; RACHMILEWITZ, D.; KLEIN, J. S.; FIOCCHI, C. Localization of intestinal interleukin 1 activity and protein and gene expression to lamina propria cells. **Gastroenterology**, v. 104, p. 749–758, 1993.

YIRMIYA, R. Endotoxin produces a depressive-like episode in rats. **Brain Research**, v. 711, p. 163-174, 1996.

YIRMIYA, R.; POLLAK, Y.; BARAK, O.; AVITSUR, R.; OVADIA, H.; BETTE, M.; WEIHE, E.; WEIDENFELD, J. Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents. **Neuropsychopharmacology**, v. 24, p. 531- 544, 2001.

ZAGER, A.; PERON, J. P.; MENNECIER, G.; RODRIGUES, S. C.; ALOIA, T. P.; PALERMO-NETO, J. Maternal immune activation in late gestation increases neuroinflammation and aggravates experimental autoimmune encephalomyelitis in the offspring. **Brain Behavior Immunology**, v. 43, p. 159-171, 2015.

ZENEWICZ, L. A.; ANTOV, A.; FLAVELL, R. A. CD4 T-cell differentiation and inflammatory bowel disease. **Trends in Molecular Medicine**, v. 15, p. 199- 207, 2009.