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**BIBLIOGRAPHY**

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1. Bantam: The Bantam Medical Dictionary. Bantam Books, Toronto, 1990.
2. Totoro GJ: Principles of Anatomy and Physiology, 8th ed. HarperCollins, New York, 1996
3. Arthur S. Schneider, Philip A. Szanto, Pathology, 3<sup>rd</sup> edition, Blackwell Science, 2002.
4. Florey: General Pathology. Third Edition, W. B. Saunders Company, 1962.
5. Kumar, Abbas, Fausto: Robbins and Contran Pathologic Basis of Disease. Elsevier-Saunders, Seventh Edition, 2005.
6. Schumacher RH Jr ed.: Primer on the Rheumatic Diseases, 10th ed. Arthritis Foundation, Atlanta, 1993
7. Blower AL: Considerations for nonsteroidal anti-inflammatory drug therapy: Safety. Scandinavian Journal of Rheumatology 1996; vol. 25 (suppl. 105): 13-26
8. Pouvourville G: The iatrogenic cost of non-steroidal anti-inflammatory drug therapy. British Journal of Rheumatology 1995; vol. 34 (suppl. 1): 19-24
9. Canada NewsWire: Clinical trials show new prescription drug provides relief from arthritis pain. Dimethaid Research Inc. [press release] February 23 1996.
10. Fries J: Toward an understanding of NSAID-related adverse events: The contribution of longitudinal data. Scandinavian Journal of Rheumatology 1996; vol. 25 (suppl. 102): 3-8
11. Emery P: Considerations for nonsteroidal anti-inflammatory drug therapy: Benefits. Scandinavian Journal of Rheumatology 1996; vol. 25 (suppl. 105): 5-12
12. Tannenbaum H, Davis P, Russell AS, Atkinson MH, Maksymowych W, Huang SH, Bell M, Hawker GA, Juby A, Vanner S, Sibley J: An evidence-based approach to prescribing NSAIDs in musculoskeletal disease: a Canadian consensus. Canadian Medical Association Journal 1996; vol. 155: 77-88.
13. Vane JR: Mechanism of action of NSAIDs. British Journal of Rheumatology 1996; vol. 35 (suppl. 1): 1-3.
14. Emery P: Clinical implications of selective cyclooxygenase-2 inhibition. Scandinavian Journal of Rheumatology 1996; vol. 25 (suppl. 102): 23-28.
15. Reuters: Aspirin protocol for prevention of cardiovascular disease questioned. Reuters Medical News, January 13 1997.
16. S.SENGUPTA; CYCLOOXYGENASE-2: A NEW THERAPEUTIC TARGET, Indian Journal of Pharmacology 1999; 31: 322-332.

17. Bruce M., Curt D, Furberg, COX-2 Inhibitors — Lessons in Drug Safety, *n engl j med* 352;11,17, 2005.
18. Patricia McGettigan, David Henry, Cardiovascular Risk and Inhibition of Cyclooxygenase A Systematic Review of the Observational Studies of Selective and Nonselective Inhibitors of Cyclooxygenase 2, *JAMA*, October 4, 2006—Vol 296, No. 13.
19. Hawkey CJ: Non-steroidal anti-inflammatory drug gastropathy: causes and treatment. *Scandinavian Journal of Gastroenterology* 1996; vol. 220: 124-7.
20. Reuters: Coated aspirin doesn't prevent GI bleeding. Reuters Health eLine, November 22 1996.
21. Searle: FDA committee recommends changes in NSAID labeling. [press release] G.D. Searle & Co., October 12 1995.
22. Reuters: Aspirin linked to GI perforation. Reuters Health eLine, March 10 1997.
23. National Institutes of Health: Stomach and duodenal ulcers. National Institutes of Health (United States), Publication #95-38, 1995. <http://www.gastro.com/ulcers.htm>
24. IFHII: About Helicobacter pylori. International Foundation for Helicobacter and Intestinal Immunology 1997. <http://www.helico.com/web/pylorweb.html>
25. Neustater BR, Barkin JS: Non-steroidal anti-inflammatory drugs (NSAID) cause gastrointestinal ulcers mainly in Helicobacter pylori carriers. *Gastrointestinal Endoscopy* 1995; vol. 41: 186-7
26. Reuters: H2-Receptor blockers and antacids may not protect against GI effects of NSAIDs. Reuters Medical News, July 29 1996.
27. Reuters: NSAIDs associated with quadruple the risk of acute renal failure. Reuters Medical News, December 17 1996.
28. Reuters: NSAIDs cause GI bleeding. Reuters Health eLine, December 20 1996.
29. Searle: Antacids and acid blockers found to be ineffective in preventing gastrointestinal damage in arthritis patients. [press release] G.D. Searle & Co., July 22
31. Searle: Popular drugs for GI problems may increase risk of serious complications in arthritis patients. [press release] G.D. Searle & Co., October 8 1996.
32. Searle: Studies raise questions about antacid use. [press release] G.D. Searle & Co., October 23 1995.

33. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF: Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. *Archives of Internal Medicine* 1996; vol. 156: 1530-36
34. Taha AS et al: Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal anti-inflammatory drugs. *New England Journal of Medicine* 1996; vol. 334: 1435-1439
35. Walsh JH: Unanswered questions about *Helicobacter pylori*. *Ailment Pharmacol Ther.* 1995; vol 9 suppl. 1: 31-7
- 36 Wallace JL, Reuter BK, Cicala C, McKnight W, Grisham MB, Cirino G. Novel nonsteroidal anti-inflammatory drug derivatives with markedly reduced ulcerogenic properties in the rat. *Gastroenterology* 1994; 107: 172-179.
- 37 Berman B (ed): *Willow Bark*. Baltimore: University of Maryland Medical Center 2004.
- 38 Hitti M: Timeline of pain reliever controversy, tracing the path on Cox-2, NSAID pain relievers. *WebMD Medical News*, April 7, 2005.
- 39 Zandi E, Karin M: Bridging the gap: composition, regulation, and physiological function of the I $\kappa$ B kinase complex. *Mol Cell Biol* 19:4547–4551, 1999
- 40 Jarvinen M: Healing of a crush injury in rat striated muscle. *Acta Chir Scand* 142:47–56, 1976
- 41 Curtis CL, Harwood JL, Dent CM, Caterson B: Biological basis for the benefit of nutraceutical supplementation in arthritis. *Drug Discov Today* 9:165–172, 2004
- 42 Curtis CL, Hughes CE, Flannery CR, Little CB, Harwood JL, Caterson B: n-3 fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. *J Bio Chem* 275:721–724, 2000
- 43 Curtis CL, Rees SG, Little CB, Flannery CR, Hughes CE, Wilson C, et al: Pathologic indicators of degradation and inflammation in human osteoarthritic cartilage are abrogated by exposure to n-3 fatty acids. *Arthritis Rheum* 46:1544–1553, 2002
- 44 Daviglius ML, Stamler J, Orenca AJ, Dyer AR, Liu K, Greenland P, et al: Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med* 336:1046–1053, 1997
45. Chrubasik S, Eisenberg E, Balan E, Weinberger T, Luzzati R, Conradt C: Treatment of low back pain exacerbations with willow bark extract: a randomized double blind study. *Am J Med* 9:9–14, 2000

- 46 Badria FA, El-Farahaty T, Shabana AA, Hawas SA, El-Batoty MF: Boswellia-curcumin preparation for treating knee osteoarthritis: a clinical evaluation. *Alt Complement Ther* 8: 341–348, 2002
- 47 Bengmark S: Curcumin, an atoxic antioxidant and natural NF $\kappa$ B, cyclooxygenase-2, lipoxygenase, and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases. *JPEN J Parenter Enteral Nutr* 30:45–51, 2006
- 48 Natarajan C, Bright JJ: Curcumin inhibits experimental allergic encephalomyelitis by blocking IL-12 signaling through Janus Kinase-STAT pathway in T lymphocytes. *J Immunol* 168: 6506–6513, 2002
- 49 Adcocks C, Collin P, Buttle DJ: Catechins from green tea (*Camellia sinensis*) inhibit bovine and human cartilage proteoglycan and type II collagen degradation *in vitro*. *J Nutr* 132: 341–346, 2002
- 50 Haqqi TM, Anthony DD, Gupta S, Ahmad N, Lee MS, Kumar GK, et al: Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea. *Proc Natl Acad Sci U S A* 96:4524–4529, 1999
- 51 Hollman PC, Feskens EJ, Katan MB: Tea flavonols in cardiovascular disease and cancer epidemiology. *Proc Soc Exp Biol Med* 220:198–202, 1999
- 52 Araghi-Niknam M, Hosseini S, Larson D, Rohdewald P, Watson RR: Pine bark extract reduces platelet aggregation. *Integr Med* 2:73–77, 2000
- 53 Grimm T, Chovanová Z, Muchová J, Sumegová K, Liptáková A, Durackova Z, et al: Inhibition of NF- $\kappa$ B activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol). *J Inflamm* 3: 1, 2006
- 54 Anonymous: *Boswellia serrata*. *Altern Med Rev* 3:306–307, 1998
- 55 Kulkarni RR, Patki PS, Jog VP, Gandage SG, Patwardhan B: Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study. *J Ethnopharmacology* 33:91–95, 1991
- 56 Hilepo JN, Bellucci, Mossey RT: Acute renal failure caused by "cat's claw" herbal remedy in a patient with systemic lupus erythematosus. *Nephron* 77:361, 1997
- 57 Piscoya J, Rodriguez Z, Bustamante SA, Okuhama NN, Miller MJS, Sandoval M, et al: Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: mechanisms of action of the species *Uncaria guianensis*. *Inflamm Res* 50:442–448, 2001

- 58 Sandoval M, Charbonnet RM, Okuhama NN, Roberts J, Krenova Z, Trentacosti AM, et al: Cat's claw inhibits TNF- production and scavenges free radicals: role in cytoprotection. *Free Radic Biol Med* 29:71–78, 2000
- 59 Bernstein JE, Bickers DR, Dahl MV, Roshal JY: Treatment of chronic postherpetic neuralgia with topical capsaicin. A preliminary study. *J Am Acad Dermatol* 17:93–98, 1987.
- 60 Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitzi KR, et al: Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* 288:306–313, 2000.
61. Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Bloch DA: Toward an epidemiology of gastropathy associated with Nonsteroidal anti-inflammatory drug use. *Gastroenterology* 1989,Suppl:647-655.
62. Rahme E, Marentette MA, Kong SX, Leloirier J: Use of NSAIDs, COX-2 inhibitors, and acetaminophen and associated coprescriptions of gastroprotective agents in an elderly population. *Arthritis Rheum* 2002, 47:595-602.
63. Abramson SB, Weaver AL: Current state of therapy for pain and inflammation. *Arthritis Research & Therapy* 2005, 7(suppl 4):S1-S6. 4. Dubois RW, Melmed GY, Henning JM, Laine L: Guidelines for the appropriate use of non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2-specific inhibitors and proton pump inhibitors in patients requiring chronic anti-inflammatory therapy. *Aliment Pharmacol Ther* 2004, 19:197-208.
64. Gabriel SE, Jaakkimainen L, Bombardier C: Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991, 115:787-796.
65. Singsh G, Triadafilopoulos G: Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol* 1999, Suppl 56:18-24.
66. Laine L: Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001, 120:594-606.
67. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, Geis GS: Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995, 123:241-249.

68. Coles LS, Fries JF, Kraines RG, Roth SH: From experiment to experience: side effects of nonsteroidal anti-inflammatory drugs. *Am J Med* 1983, 74:820-828.
69. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, *et al.*: Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-Term Arthritis Safety Study. *JAMA* 2000, 284:1247-1255.
70. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, *et al.*: Comparison of upper gastrointestinal toxicity of rofecoxib and
71. naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000, 343:1520-1528.
72. Fries JF, Murtagh KN, Bennett M, Zatarain E, Lingala B, Bruce B: The rise and decline of nonsteroidal anti-inflammatory drug-associated gastropathy in rheumatoid arthritis. *Arthritis Rheum* 2004, 50:2433-2440.
73. Cryer B: Nonsteroidal anti-inflammatory drugs and gastrointestinal disease. In *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. Edited by Feldman M, Scharschmidt BF;
74. Sleisenger M. Philadelphia, PA: WB Saunders Co; 1998:343-357.
75. Talley NJ, Evans JM, Fleming KC, Harmsen WS, Zinsmeister AR, Melton LJ III: Nonsteroidal anti-inflammatory drugs and dyspepsia in the elderly. *Dig Dis Sci* 1995, 40:1345-1350.
76. Huang JQ, Sridhar S, Hunt RH: Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic ulcer disease: a meta-analysis. *Lancet* 2002, 359:14-22.
77. Scheiman JM: NSAIDs, gastrointestinal injury, and cytoprotection. *Gastroenterol Clin North Am* 1996, 25:279-298.
78. Scheiman JM: Effects of nonsteroidal anti-inflammatory drugs, including COX-2 specific inhibitors, on the GI tract. Clinical update. *Am Soc Gastrointest Endosc* 2005, 13:1-4.
79. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines: Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002, 46:328-346.

80. Garcia Rodriguez LA, Jick H: Risk of upper gastrointestinal bleeding and perforation associated with individual Nonsteroidal anti-inflammatory drugs. *Lancet* 1994, 343:769-772.
81. Singh G: Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. *Arthritis, Rheumatism, and Aging Medical Information System. Am J Ther* 2000, 7:115-121.
82. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF: Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch Intern Med* 1996, 156:1530-1536.
83. Scheiman JM, Bandekar RR, Chernew ME, Fendrick AM: *Helicobacter pylori* screening for individuals requiring chronic NSAID therapy: a decision analysis. *Aliment Pharmacol Ther* 2001, 15:63-71.
84. Peura D: The problem of *Helicobacter pylori*-negative idiopathic ulcer disease. *Baillieres Best Pract Res Clin Gastroenterol* 2000, 14:109-117.
85. Chan FK, Chung SC, Suen BY, Lee YT, Leung WK, Leung VK, Wu JC, Lau JY, Hui Y, Lai MS, *et al.*: Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med* 2001, 344:967-973. *Arthritis Research & Therapy* September 2005 Vol 7 Suppl 4 Peura and Goldkind S13
86. Henry D, Lim LL, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, *et al.*: Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996, 312:1563-1566.
87. Garcia Rodriguez LA, Hernandez-Diaz S: Risk of uncomplicated peptic ulcer among users of aspirin and nonaspirin Nonsteroidal anti-inflammatory drugs. *Am J Epidemiol* 2004, 159:23- 31.
88. Eidelman RS, Hebert PR, Weisman SM, Hennekens CH: An update on aspirin in the primary prevention of cardiovascular disease. *Arch Intern Med* 2003, 163:2006-2010.
89. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Greenland P, Grundy SM, *et al.*: AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel

- guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002, 106:388-391.
90. Levy M, Miller DR, Kaufman DW, Siskind V, Schwingl P, Rosenberg L, Strom B, Shapiro S: Major upper gastrointestinal tract bleeding. Relation to the use of aspirin and other nonnarcotic analgesics. *Arch Intern Med* 1988, 148:281-285.
  91. Sorensen HT, Mellemkjaer L, Blot WJ, Nielsen GL, Steffensen FH, McLaughlin JK, Olsen JH: Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol* 2000, 95:2218-2224.
  92. Laine L: Proton pump inhibitor co-therapy with Nonsteroidal anti-inflammatory drugs: nice or necessary? *Rev Gastroenterol Disord* 2004, Suppl 4:S33-S41.
  93. Garcia Rodriguez LA, Hernandez-Diaz S: Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. *Epidemiology* 2001, 12:570-576.
  94. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR: Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full *in vitro* analysis. *Proc Natl Acad Sci USA* 1999, 96:7563-7568.
  95. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, Moskowitz RW, Schnitzer TJ: Guidelines for medical management of osteoarthritis. Part II. Osteoarthritis of the knee. *Arthritis Rheum* 1995, 38:1541-1546.
  96. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, Moskowitz RW, Schnitzer TJ: Guidelines for the medical management of osteoarthritis. Part I. Osteoarthritis of the hip. *Arthritis Rheum* 1995, 38:1535-1540.
  97. Pincus T, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, Wolfe F, Gibofsky A, Simon L, Zlotnick S, *et al.*: Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis* 2004, 63:931-939.
  100. Case JP, Baliunas AJ, Block JA: Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. *Arch Intern Med* 2003, 163:169-178.

101. Wolfe F, Zhao S, Lane N: Preference for nonsteroidal anti-inflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *Arthritis Rheum* 2000, 43:378-385.
102. Lee C, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ: A comparison of the efficacy and safety of nonsteroidal anti-inflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. *Arthritis Rheum* 2004, 51:746-754.
103. Zhang W, Jones A, Doherty M: Does paracetamol (acetaminophen) reduce the pain of osteoarthritis?: a meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2004, 63:901- 907.
104. Garcia Rodriguez LA, Williams R, Derby LE, Dean AD, Jick H: Acute liver injury associated with nonsteroidal anti-inflammatory drugs and the role of risk factors. *Arch Intern Med* 1994, 154:311-316.
105. Carson JL, Strom BL, Duff A, Gupta A, Das K: Safety of Nonsteroidal anti-inflammatory drugs with respect to acute liver disease. *Arch Intern Med* 1993, 153:1331-1336.
106. Graham GG, Scott KF, Day RO: Tolerability of paracetamol. *Drug Saf* 2005, 28:227-240.
107. Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil OA, Hay JE, Hynan L, *et al.*; U.S. Acute Liver Failure Study Group: Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002, 137:947-954.
108. Center for Drug Evaluation and Research, Food and Drug Administration: Joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, volume III [transcript]. [<http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4090T3.htm>]
109. US Food and Drug Administration, Center for Drug Evaluation and Research: COX-2 selective (includes Bextra, Celebrex, and Vioxx) and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). [<http://www.fda.gov/cder/drug/infopage/cox2/default.htm>]

110. Borer JS, Simon LE: Cardiovascular and gastrointestinal effects of COX-2 inhibitors and NSAIDs: achieving a balance. *Arthritis Research & Therapy* 2005, 7(suppl 4):S14-S22.
111. Bocanegra TS, Weaver AL, Tindall EA, Sikes DH, Ball JA, Wallemark CB, Geis GS, Fort JG, and the Arthrotec Osteoarthritis Study Group: Diclofenac/misoprostol compared with diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized, placebo controlled trial. *J Rheumatol* 1998, 25:1602-1611.
112. Graham DY, White RH, Moreland LW, and the Misoprostol Study Group: Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDs. *Ann Intern Med* 1993, 119:257-262.
113. Cullen D, Bardhan KD, Eisner M, Kogut DG, Peacock RA, Thomson JM, Hawkey CJ: Primary gastroduodenal prophylaxis with omeprazole for non-steroidal anti-inflammatory drug users. *Aliment Pharmacol Ther* 1998, 12:135-140.
114. Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, Yeomans ND. and the Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group: Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1998, 338:727-734.
115. Lanas A, Rodrigo L, Marquez J, Bajador E, Perez-Roldan F, Cabrol J, Quintero E, Montoro M, Gomollon F, Santolaria S, *et al.*; EMPHASYS Study Group: Low frequency of upper gastrointestinal complications in a cohort of high-risk patients taking low-dose aspirin or NSAIDs and omeprazole. *Scand J Gastroenterol* 2003, 38:693-700.
116. Chan FK, Hung LC, Suen BY, Wong VW, Hui AJ, Wu JC, Leung WK, Lee YT, To KF, Chung SC, *et al.*: Celecoxib versus diclofenac plus omeprazole in high-risk arthritis patients: results of a randomized double-blind trial. *Gastroenterology* 2004, 127:1038-1043.
117. cheiman JM, Fendrick AM: Practical approaches to minimizing gastrointestinal and cardiovascular safety concerns with COX-2 inhibitors and NSAIDs. *Arthritis Research & Therapy* 2005, 7(suppl 4):S23-S29..
118. Bresalier RS, Sandler RS, Quan H, *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102.

119. Farkouh ME, Kirshner H, Harrington RA, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004;364:675–84.
120. White WB, Strand V, Roberts R, Whelton A. Effects of the cyclooxygenase-2 specific inhibitor valdecoxib versus nonsteroidal anti-inflammatory agents and placebo on cardiovascular thrombotic events in patients with arthritis. *Am J Ther* 2004;11:244–50.
121. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* 2004;109:2068–73.
122. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004;364:2021–9.
123. Solomon DH, Schneeweiss S, Levin R, Avorn J. Relationship between COX-2 specific inhibitors and hypertension. *Hypertension* 2004;44:140–5.
124. Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM. Cyclooxygenase-2 specific inhibitors and cardiorenal function: a randomised, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther* 2001;8:85–95.
125. Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population based cohort study. *Lancet* 2004;363:1751–6.
126. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case control study. *Lancet* 2005;365:475–81.
127. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case control analysis. *BMJ* 2005;330:1366.

128. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071–80.
129. Campen DH, Graham D, Cheetham C, et al. Risk of acute cardiac events among patients treated with cyclooxygenase-2 selective and nonselective nonsteroidal anti-inflammatory drugs. *Arthritis Rheum* 2004;50(9 Suppl):S657/1756.
130. Layton D, Heeley E, Hughes K, Shakir SA. Comparison of the incidence rates of thromboembolic events reported for patients prescribed rofecoxib and meloxicam in general practice in England using prescription event monitoring (PEM) data. *Rheumatology (Oxford)* 2003;42:1342–53.
131. Layton D, Hughes K, Harris S, Shakir SA. Comparison of the incidence rates of thromboembolic events reported for patients prescribed celecoxib and meloxicam in general practice in England using Prescription-Event Monitoring (PEM) data. *Rheumatology (Oxford)* 2003;42:1354–64.
132. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005;352:1081–91.
133. Curtis SP, Mukhopadhyay S, Ramey D, Reicin A. Cardiovascular safety summary associated with the etoricoxib development program. *Arthritis Rheum* 2003;48(Suppl 9):S616.
134. Singh G, Mithal A, Triadafilopoulos G. Both selective COX-2 inhibitors and non-selective NSAIDs increase the risk of acute myocardial infarction in patients with arthritis: selectivity is with the patient, not the drug class. *Ann Rheum Dis* 2005;64(Suppl III):85. Abstract.
135. Fitzgerald GA. Coxibs and Cardiovascular Disease. *N Engl J Med* 2004;351:1709–11.
136. Brater DC, Harris C, Redfern JS, Gertz BJ. Renal effects of COX-2-selective inhibitors. *Am J Nephrol* 2001;21:1–15.
137. Curtis SP, Ng J, Yu Q, et al. Renal effects of etoricoxib and comparator nonsteroidal anti-inflammatory drugs in controlled clinical trials. *Clin Ther* 2004;26:70–83.
138. Krum H, Liew D, Aw J, Haas S. Cardiovascular effects of selective cyclooxygenase-2 inhibitors. *Expert Rev Cardiovasc Ther* 2004;2:265–70.

139. Baker CS, Hall RJ, Evans TJ, et al. Cyclooxygenase-2 is widely expressed in atherosclerotic lesions affecting native and transplanted human coronary arteries and colocalises with inducible nitric oxide synthase and nitrotyrosine particularly in macrophages. *Arterioscler Thromb Vasc Biol* 1999;19:646–55.
140. Widlansky ME, Price DT, Gokce N, et al. Short and long term COX-2 inhibition reverses endothelial dysfunction in patients with hypertension. *Hypertension* 2003;42:310–5.
141. Chenevard R, Hurlimann D, Bechir M, et al. Selective COX-2 inhibition improves endothelial function in coronary artery disease. *Circulation* 2003;107:405–9.
142. Monakier D, Mates M, Klutstein MW, et al. Rofecoxib, a COX-2 inhibitor, lowers C-reactive protein and interleukin-6 levels in patients with acute coronary syndromes. *Chest* 2004;125:1610–5.
143. J. J. Li, G. D. Anderson, E. G. Burton, J. N. Cogburn, J. T. Collins, D. J. Garland, S. A. Gregory, H. C. Huang, P. C. Isakson, C. M. Koboldt, E. W. Logusch, M. B. Norton, W. E. Perkins, E. J. Reinhard, K. Seibert, A. W. Veenhuizen, Y. Zhang and D. B. Reitz, 1,2-Diarylcyclopentenes as selective cyclooxygenase-2 inhibitors and orally active anti-inflammatory agents, *J. Med. Chem.* **38** (1995) 4570–4578.
144. T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, F. J. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. A. Anderson, F. G. Burton, J. N. Cogburn, S. A. Gragory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang and P. C. Isakson, Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: Identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib), *J. Med. Chem.* **40** (1997) 1347–1365.
145. G. Dannhardt and W. Kiefer, Cyclooxygenase inhibitors – current status and future prospects, *Eur. J. Med. Chem.* **36** (2001) 109–126.
146. P. Prasit, Z. Wang, C. Brideau, C. C. Chan, S. Charleson, W. Cromlish, D. Either, J. F. Evans, A. W. Ford-Hutchinson, J. Y. Gauthier, R. Gordon, J. Guay, M. Gresser, S. Kargman, B. Kennedy, Y. Leblanc, S. Leger, J. Mancini, G. P. O’Neil, M. Ouellet, M. D. Percieval, H. Perrier, D. Riendeau, I. Rodger, P. Tagari, M. Therien, P. Vickers, E. Wong, L. J. Xu, R. N. Young, R. Zamboni, S. Boyce, N. Rupniak, M. Forrest, D. Visco and D. Patrick, The discovery of rofecoxib, [MK 966, VIOXX®, 4-

- (4'-methylsulfonylphenyl)-3-phenyl-2(5*H*)-furanone], an orally active cyclooxygenase-2 inhibitor, *Bioorg. Med. Chem. Lett.* **9** (1999) 1773–1778.
147. J. J. Tally, D. L. Brown, J. S. Carter, M. J. Graneto, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, R. S. Rogers, A. F. Shaffer, Y. Y. Zhang, B. S. Zweifel and K. Seibert, 4-[5-Methyl-3-phenylisoxazol-4-yl]-benzenesulfonamide, valdecoxib: A potent and selective inhibitor of COX-2, *J. Med. Chem.* **43** (2000) 775–777.
148. J. J. Tally, S. R. Bertenshaw, D. L. Brown, J. S. Carter, M. J. Graneto, M. S. Kellogg, C. M. Koboldt, J. Yuan, Y. Y. Zhang and K. Seibert, *N*-[[5-Methyl-3-phenylisoxazol-4-yl]-phenyl]sulfonyl]propanamide, sodium salt, parecoxib sodium: A potent and selective inhibitor of COX-2 for parenteral administration, *J. Med. Chem.* **43** (2000) 1661–1663.
149. D. Riendeau, M. D. Percieval, C. Brideau, S. Charleson, D. Dube, D. Ethier, J. P. Falguyret, R. W. Friesen, R. Gordon, G. Greig, J. Guay, J. Mancini, M. Ouellet, E. Wong, L. J. Xu, S. Boyce, D. Visco, Y. Girard, P. Prasit, R. Zamboni, I. W. Rodger, M. Gresser, A. W. Ford-Hutchinson, R. N. Young and C. C. Chan, Etoricoxib (MK-0663): Preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2, *J. Pharmacol. Exp. Ther.* **296** (2001) 558–570.
150. M. R. Yadav, R. Giridhar and H. B. Prajapati, *A Process for Preparation of 3-[o-/m-/p-Mono/DisubstitutedPhenyl]- 4-[o-/p-Substitutedphenyl]furazans and Furoxans*, Indian Patent Appl. No. 109/MUM/2004, Feb. 2004.
151. H. Cerecetto and W. Porcal, Pharmacological properties of furoxans and benzofuroxans: Recent developments, *Mini-Rev. Med. Chem.* **5** (2005) 57–71.
152. V. G. Granik and N. B. Grigor, Nitric oxide synthase inhibitors: Biology and Chemistry, *Russ. Chem. Bull.* **51** (2002) 1973–1995.
153. C. Velazquez, P. N. P. Rao, R. McDonald and E. E. Knaus, Synthesis and biological evaluation of 3,4-diphenyl-1,2,5-oxadiazole-2-oxides and 3,4-diphenyl-1,2,5-oxadiazoles as potential hybrid COX-2 inhibitor/nitric oxide donor agents, *Bioorg. Med. Chem.* **13** (2005) 2749–2757.
154. Majithiya JB, Balaraman R, Giridhar R, Yadav MR. Effect of bis[curcumino] - oxovanadium complex on non-diabetic and streptozotocin-induced diabetic rats. *J Trace Elem Med Biol.* 2005;18(3):211-7.

155. Hattori K, Sukenobu N, Sasaki T, Takasuga S, Hayashi T, Kasai R, Yamasaki K, Hazeki O. Activation of insulin receptors by lagerstroemin. *J Pharmacol Sci.* 2003 Sep;93(1):69-73.
156. Kulkarni SK, Dhir A. *Withania somnifera*: An Indian ginseng Prog Neuropsychopharmacol Biol Psychiatry. 2007 Sep 21.
157. Ayurvedic Herbs for Longevity and Rejuvenation by Dr H. S. Puri (2003), published by Taylor & Francis, London, pages 43-45.
158. Miller AL (1998). "Botanical influences on cardiovascular disease". *Altern Med Rev* 3 (6): 422-31.
159. Devi RS, Narayan S, Vani G, Shyamala Devi CS (2007). "Gastroprotective effect of Terminalia arjuna bark on diclofenac sodium induced gastric ulcer." *Chem Biol Interact* 167 (1): 71-83.
161. Mertens-Talcott SU, Jilma-Stohlawetz P, Rios J, Hingorani L, Derendorf H. Absorption, metabolism, and antioxidant effects of pomegranate (*Punica granatum* L.) polyphenols after ingestion of a standardized extract in healthy human volunteers. *J Agric Food Chem.* 2006 Nov 15;54(23):8956-61.
161. Aviram M, Dornfeld L. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure *Atherosclerosis* 2001 Sep;158(1):195-8.
162. Seeram NP, Aronson WJ, Zhang Y et al. Pomegranate ellagitannin-derived metabolites inhibit prostate cancer growth and localize to the mouse prostate gland. *J Agric Food Chem.* 2007 Sep 19;55(19):7732-7.
163. Omar, S., et al. "Hypoglycemic effect of the seeds of *Momordica charantia*." *Fitoterapia.* 2007; 78(1): 46-7.
164. Ojewole, J., et al. "Hypoglycaemic and hypotensive effects of *Momordica charantia* Linn (Cucurbitaceae) whole-plant aqueous extract in rats." *Cardiovasc. J. S. Afr.* 2006 Sep-Oct; 17(5): 227-32.
165. Zhang, Q. C. "Preliminary report on the use of *Momordica charantia* extract by HIV patients." *J. Naturopath. Med.* 1992; 3: 65-9.
166. Prakash P, Gupta N. Therapeutic uses of *Ocimum sanctum* Linn (Tulsi) with a note on eugenol and its pharmacological actions: a short review.

167. Jyoti Sethi, Sushma Sood, Shashi Seth, and Anjana Talwar. Evaluation of Hypoglycemic and Antioxidant Effect of *Ocimum Sanctum*,. *Indian Journal of Clinical Biochemistry*, 2004, 19 (2) 152-155.
168. Sharma, P; Kulshreshtha, S; Sharma, A L. Anti-cataract activity of *Ocimum sanctum* on experimental cataract. *Indian Journal of Pharmacology*, v.30, n.1, 1998:16-20.
169. Murphy, Sean. "Wheatgrass, healthy for the body and the bank account", *ABC Landline*, 2002-10-13. Retrieved on 2006-10-06.
170. Ben-Arye, E & Goldin, E (2002 Apr), "Wheat grass juice in the treatment of active distal ulcerative colitis: a randomized double-blind placebo-controlled trial.", *Scand J Gastroenterol* (Norway) Volume 37 (Issue 4): Pages 444-9.
171. de Vogel, Johan; Denise S. M. L. Jonker-Termont, Martijn B. Katan, and Roelof van der Meer (August 2005). "Natural Chlorophyll but Not Chlorophyllin Prevents Heme-Induced Cytotoxic and Hyperproliferative Effects in Rat Colon". *J. Nutr.* 135: 1995-2000. The American Society for Nutritional Sciences. □
172. Ferruzzia, Mario G. & Blakesleeb, Joshua (January 2007), "Digestion, absorption, and cancer preventative activity of dietary chlorophyll derivatives", *Nutrition Research* Volume 27 (Issue 1): Pages 1-12 .
173. Title LM, Giddens K, McInerney MM, McQueen MJ, Nassar BA. Effect of cyclooxygenase-2 inhibition with rofecoxib on endothelial dysfunction and inflammatory markers in patients with coronary artery disease. *J Am Coll Cardiol* 2003;42:1747-53.
174. Maxey, K.M., Maddipati, K.R. and Birkmeier, J. Interference in enzyme immunoassays. *J. Clin. Immunoassay* 1992 15, 116-120.
175. Otterness, I.G., Moore, P.F., Carrageenan foot edema test. *Methods SEnzymol.* 1988, 162, 320-327.
176. C.C. Chan et al, Rofecoxib( Vioxx, MK-0966; 4-(4' -ethylsulfonylphenyl)-3-phenyl-2-(5H)-furanone): A Potent and orally active Cyclooxygenase-2 Inhibitor, Pharmacological and Biochemical Profiles. *JPET* 290:551-560, 1999.
177. Tran C.P., Cook, G.A., Yeomans, N.D., Thim, L., Giraud, A.S. (1999), Trefoil peptide TFF2 potently accelerates healing and reduces inflammation in a rat model of colitis, *Gut*;44;;636-642.

178. Di stasi, L.C., Cotal, M., Sigrid L.S. Mendacolli M, (1988):. Screening in Mice of some medicinal plants used for analgesic purposes in the state of Sao Paulo J. of Ethnopharmacol 24:205-211.
179. Seigmund, E., Cadmus, R., and Lu, G. A method for evaluation of both non-narcotic and narcotic analgesics. Proc. Soc. Exp. Biol. Med. 1957,95, 729.
180. Chan, C.C., Boyce, S., Brideau, C., Ford-Hutchinson, A.W., Gordon R., Guay, D., Hill, R.G., Li, C.S., Mancicni, J., Penneton, M. *et al.*, 1995. Pharmacology of a selective cyclooxygenase-2 inhibitor, L-745,337: a novel nonsteroidal anti-inflammatory agent with an ulcerogenic sparing effect in rat and nonhuman primate stomach. *J. Pharmacol. Exp. Ther.* 274, pp. 1531–1537.
181. Maritto, S., Menegazzi, M., Carceran De Prati, A., Cuzzolin, L., Adami, A., Suzuki, H. & Benoni, G. Protective effect of NO on gastric lesions and inhibition of expression of gastric inducible NOS by flurbiprofen and its nitroderivative, nitroflurbiprofen. *Br. J. Pharmacol.*, (1995). 116, 1713- 1714
182. Daniela S. Hauser, Matthias Stade, Angela Schmidt, Guido Hanauer, Cardiovascular parameters in anaesthetized guinea pigs: A safety pharmacology screening model *Journal of Pharmacological and Toxicological Methods* 52 (2005) 106– 114.
183. de Groot, Annemieke A.; Mathy, Marie-Jeanne; van Zwieten, Pieter A.; Peters, Stephan L. M. Involvement of the [beta]3 Adrenoceptor in Nebivolol-Induced Vasorelaxation in the Rat Aorta, *Journal of Cardiovascular Pharmacology.* 42(2):232-236, August 2003.
184. Jones BJ, Roberts DJ, The quantitative measurement of motor inco-ordination in naïve mice using an accelerating rotarod. *J Pharm Pharmac* 20: 302–304, 1968.
185. Naidu, P.S., Kulkarni, S.K. Quercetin, a bioflavonoid, reverses haloperidol-induced catalepsy *Methods Find Exp Clin Pharmacol* 2004, 26(5): 323
186. Viswanatha Swamy, Thippeswamy, Manjula. and Mahendra Kumar C.B4 Some Neuropharmacological Effects of the Methanolic Root Extract of *Cissus Quadrangularis* in Mice *African Journal of Biomedical Research*, Vol. 9 (2006); 69 - 75
187. Irvine, F. R. Woody plants of Ghana, Oxford University Press, London, (1961),962-965.

188. Guidance for Industry, Toxicity Testing for Pharmaceuticals, *Centre of Drug Evaluation and Research(CDER)*, August 1996., Internet Edition, fda, USA.
189. OECD GUIDELINE FOR THE TESTING OF CHEMICALS : Acute Oral Toxicity – Fixed Dose Procedure, December 2001, Internet Edition.
190. OECD GUIDELINE FOR THE TESTING OF CHEMICAL: Repeated Dose 28-day Oral Toxicity Study in Rodents, July 1995, Internet edition.
191. C.W. Murray, F. Porreca and A. Cowan, Methodological refinements in the mouse paw formalin test an animal model of tonic pain. *Journal of Pharmacological Methods* **20** (1988), pp. 175–186.
192. Rang H.P., Dale, M.M., Ritter, J.M., 1995. Pharmacology. Churchill Livingstone, London.
193. BETTINI, R., GROSSI, E., RAPAZZINI, P. & GIARDINA, G. (1986). Diclofenac sodium versus acetylsalicylic acid: a randomized study in febrile patients. *J. Int. Med. Res.*, **14**, 95–100.
194. Cyclooxygenase-2<sup>\*</sup> Inhibition and Renal Function Alfred K. Pfister, Robert J. Crisalli, AND William H. Carter *Annals* 2001 **134**: 1077.
195. Bombardier C, Laine L,<sup>†</sup> Reicin A et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med.* 2000; **343**:1520-1528.
196. Kuster LI, Frolich JC. Platelet aggregation and thromboxane release induced by arachidonic acid, collagen, ADP, and platelet-activating factor following low dose acetylsalicylic acid in man. *Prostaglandins* 1986;**32**:415-423.
197. Brand, L. M., Skare, K. L., Loomans, M. E., Reller, H. H., Schwen, R. J., Lade, D. A. *et al.*  
(1990). Anti-inflammatory pharmacology and mechanism of the orally active capsaicin analogs, NE- 19550 and NE-28345. *Agents and Actions* **31**, 329–40.
198. Kumakura, S., Mishima, M., Kobayashi, S., Shirota, H., Abe, S., Yamada, K. *et al.* (1990). Inhibitory effect of indomethacin farnesil, a novel anti-inflammatory prodrug, on carrageenin- induced inflammation in rats. *Agents and Actions* **29**, 286–91.
199. Turner,R.A. Screening Methods in Pharmacology. Academic Press, London 1965.

200. R. Vinegar, J.F. Truax, J.H. Selph, P.R. Johnsstone, A.L. Venable and K.K. Mckenzie, Pathway to carrageenan-induced inflammation of the hind limb of the rat. *Federation Proceedings* **6** (1987), pp. 118–126.
201. A. Antonio and A.R.M.S. Brito, Oral anti-inflammatory and anti-ulcerogenic activities of a hydroalcoholic extract and partitioned fractions of *Turnera ulmifolia* (Turneraceae). *Journal of Ethnopharmacology* **61** (1998), pp. 215–228.
202. Hough, J.W. Nalwalk, R. Leurs, W.M.P.B. Menge and H. Timmerman, Antinociceptive activity of impentamine, a histamine congener, after CNS administration. *Life Sciences* **64** (1999), pp. 79–86.
203. M. R. Vickers and K. J. Sykes The effect of histamine on the development of adjuvant arthritis in the rat, Volume 12, Number 5 / October, 1982
204. A. Juss A. O. Olayinka, O. Onoruvwe, T. Y. Lot. Cardiovascular effects in rodents of the methanolic extract of the stem bark of *Khaya senegalensis* *Phytotherapy Research* 1987-1995 Volume 6, Issue 5 , Pages282 – 284.
205. C.T.V. Melo, A.P. Monteiro, C.P. Leite, F.L.O. Araújo, V.T. Lima and J.M. Barbosa-Filho *et al.*, Anxiolytic-Like Effects of (O-Methyl)-N-2,6-dihydroxybenzoyl-tyramine (Riparin III) from *Aniba riparia* (NEES) MEZ (Lauraceae) in Mice, *Biol Pharm Bull* **29** (3) (2006), pp. 451–454.
206. Ghosh, M.N. *Fundamentals of Experimental Pharmacology*, 2nd Edition. Scientific Book Agency, Calcutta, 1984; 154-157.