



Estudi de la biodisponibilitat del trans-resveratrol i el seu efecte quimiopreventiu del càncer de còlon induït per 1,2-dimetilhidrazina en rata

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VI. BIBLIOGRAFIA

- A**bd El-Mohsen, M., Bayele, H., Kuhnle, G., Gibson, G., Debnam, E., Kaila Sriai, S., et al. Distribution of [³H]*trans*-resveratrol in rat tissues following oral administration. *Br. J. Nutr.* 96 (1), 62-70, 2006.
- Adachi, Y., Suzuki, H., Schinkel, A.H., Sugiyama, Y. Role of breast cancer resistance protein (Bcrp1/Abcg2) in the extrusion of glucuronide and sulfate conjugates from enterocytes to intestinal lumen. *Mol. Pharmacol.* 67 (3), 923-928, 2005.
- Adesanya, S.A., Ogundana, S.K., Roberts, M.F. Dihydrostilbene phytoalexins from *Dioscorea bulbifera* and *D. dumentorum*. *Phytochemistry*. 28 (3), 773-774, 1989.
- Afaq, F., Adhami, V.M., Ahmad, N. Prevention of short-term ultraviolet B radiation-mediated damages by resveratrol in SKH-1 hairless mice. *Toxicol. Appl. Pharmacol.* 186 (1), 28-37, 2003.
- Aggarwal, B.B., Bhardwaj, A., Aggarwal, R.S., Seeram, N.P., Shishodia, S., Takada, Y. Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. *Anticancer Res.* 24 (5A), 2783-2840, 2004.
- Alfaras, I., Juan, M.E., Planas, J.M. *trans*-Resveratrol reduces precancerous colonic lesions in dimethylhydrazine-treated rats. *J. Agric. Food Chem.* 58 (13), 8104-8110, 2010.
- Alfaras, I., Pérez, M., Juan, M.E., Merino, G., Prieto, J.G., Planas, J.M., et al. Involvement of breast cancer resistance protein (BCRP1/ABCG2) in the bioavailability and tissue distribution of *trans*-resveratrol in knockout mice. *J. Agric. Food Chem.* 58 (7), 4523-4528, 2010.
- Annese, V., Valvano, M.R., Palmieri, O., Latiano, A., Bossa, F., Andriulli, A. Multidrug resistance 1 gene in inflammatory bowel disease: a meta-analysis. *World J. Gastroenterol.* 12 (23), 3636-3644, 2006.
- Arichi, H., Kimura, Y., Okuda, H., Bada, K., Kozawa, M., Arichi, S. Effects of stilbene components of the roots of *Polygonum cuspidatum* Sieb. Et Zucc. on lipid metabolism. *Chem. Pharm. Bull. (Tokyo)*. 30 (5), 1766-1771, 1982.
- Athar, M., Back, J.H., Kopelovich, L., Bickers, D.R., Kim, A.L. Multiple molecular targets of resveratrol: Anti-carcinogenic mechanisms. *Arch. Biochem. Biophys.* 486 (2), 95-102, 2009.
- Aziz, M., Kumar, R., Ahmad, N. Cancer chemopreventive by resveratrol: *in vitro* and *in vivo* studies and the underlying mechanisms (Review). *Int. J. Oncol.* 23 (1), 17-28, 2003.

- Balimane, P.V., Han, Y.H., Chong, S. Current industrial practices of assessing permeability and P-glycoprotein interaction. *AAPS J.* 8 (1), E1-E13, 2006.
- Banarjee, A., Johnston, J.S., Swaan, P.W. Carrier-mediated mechanisms for cellular drug transport. A: Lu, D.R., Øie, S., editors. *Cellular Drug Delivery: Principles and Practice*. New Jersey: Humana Press; 2004. p. 107-128.
- Bass, T.M., Weinkove, D., Houthoofd, K., Gems, D., Partridge, L. Effects of resveratrol on lifespan in *Drosophila melanogaster* and *Caenorhabditis elegans*. *Mech. Ageing Dev.* 128 (10), 546-552, 2007.
- Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*. 444 (7117), 337-342, 2006.
- Baur, J.M. Resveratrol, sirtuins, and the promise of a DR mimetic. *Mech. Ageing Dev.* 131 (4), 261-269, 2010.
- Baur, J.A., Sinclair, D.A. Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov.* 5 (6), 493-506, 2006.
- Belguendouz, L., Fremont, L., Linard, A. Resveratrol inhibits metal ion-dependent and independent peroxidation of porcine low-density lipoproteins. *Biochem. Pharmacol.* 53 (9), 1347-1355, 1997.
- Benedetti, M.S., Whomsley, R., Poggesi, I., Cawello, W., Mathy, F.X., Delporte, M.L., et al. Drug metabolism and pharmacokinetics. *Drug Metab. Rev.* 41 (3), 344-390, 2009.
- Bertelli, A.A., Das, D.K. Grapes, wines, resveratrol, and heart health. *J. Cardiovasc. Pharmacol.* 54 (6), 468-476, 2009.
- Bertelli, A.A., Gozzini, A., Stradi, R., Stella, S., Bertelli, A. Stability of resveratrol over time and in the various stages of grape transformation. *Drugs Exp. Clin. Res.* 24 (4), 207-211, 1998.
- Bird, R.P. Observation and quantification of aberrant crypts in the murine colon treated with a colon carcinogen: preliminary findings. *Cancer Lett.* 37 (2), 147-151, 1987.
- Bird, R.P. Role of aberrant crypt foci in understanding the pathogenesis of colon cancer. *Cancer Lett.* 93 (1), 55-71, 1995.
- Bisht, K., Wagner, K.H., Bulmer, A.C. Curcumin, resveratrol and flavonoids as anti-inflammatory, cyto- and DNA-protective dietary compounds. *Toxicology*. 278 (1), 88-100, 2010.

- Boocock, D.J., Patel, K.R., Faust, G.E., Normolle, D.P., Marczylo, T.H., Crowell, J.A., et al. Quantitation of *trans*-resveratrol and detection of its metabolites in human plasma and urine by high performance liquid chromatography. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 848 (2), 182-187, 2007.
- Brisdelli, F., D'Andrea, G., Bozzi, A. Resveratrol: a natural polyphenol with multiple chemopreventive properties. *Curr. Drug Metab.* 10 (6), 530-546, 2009.
- C**aderni, G., Femia, A.P., Giannini, A., Favuzza, A., Luceri, C., Salvadori, M. et al. Identification of mucin-depleted foci in the unsectioned colon of azoxymethane-treated rats: correlation with carcinogenesis. *Cancer Res.* 63 (10), 2388-2392, 2003.
- Caderni, G., Giannini, A., Lancioni, L., Luceri, C., Biggeri, A. i Dolara, P. Characterisation of aberrant crypt foci in carcinogen-treated rats: association with intestinal carcinogenesis. *Br. J. Cancer.* 71 (4), 763-769, 1995.
- Campagna, M., Rivas, C. Antiviral activity of resveratrol. *Biochem. Soc. Trans.* 38 (Pt 1), 50-53, 2010.
- Cano-Cebrián, M.J., Zornoza, T., Granero, L., Polache, A. Intestinal absorption enhancement via the paracellular route by fatty acids, chitosans and others: a target for drug delivery. *Curr. Drug Deliv.* 2 (1), 9-22, 2005.
- Cao, Z., Li, Y. Potent induction of cellular antioxidants and phase 2 enzymes by resveratrol in cardiomyocytes: protection against oxidative and electrophilic injury. *Eur. J. Pharmacol.* 489 (1-2), 39-48, 2004.
- Cardile, V., Lombardo, L., Spatafora, C., Tringali, C. Chemo-enzymatic synthesis and cell-growth inhibition activity of resveratrol analogues. *Bioorg. Chem.* 33 (1), 22-33, 2005.
- Casper, R.F., Quesme, M., Roqers, I.M., Shirota, T., Joliret, A., Milqrom, E., Savouret, J.F. Resveratrol has antagonist activity on the aryl hydrocarbon receptor: implications for prevention of dioxin toxicity. *Mol. Pharmacol.* 56 (4), 784-790, 1999.
- Chan, L.M., Lowes, S., Hirst, B.H. The ABCs of drug transport in intestine and liver: efflux proteins limiting drug absorption and bioavailability. *Eur. J. Pharm. Sci.* 21 (1), 25-51, 2004.
- Chong, J., Poutaraud, A., Hugueney, P. Metabolism and roles of stilbenes in plants. *Plant Sci.* 177 (3), 143-155, 2009.
- Ciolino, H.P., Daschner, P.J., Yeh, G.C. Resveratrol inhibits transcription of CYP1A1 in vitro by preventing activation of the aryl hydrocarbon receptor. *Cancer Res.* 58 (24), 5707-5712, 1998.

- Collett, A., Higgs, N.B., Gironella, M., Zeef, L.A., Hayes, A., Salmo, E., et al. Early molecular and functional changes in colonic epithelium that precede increased gut permeability during colitis development in mdr1a(-/-) mice. *Inflamm. Bowel Dis.* 14 (5), 620-631, 2008.
- Collins, A.R. Antioxidant intervention as a route to cancer prevention. *Eur. J. Cancer.* 41 (13), 1923-1930, 2005.
- Colom, H., Alfaras, I., Maijó, M., Juan, M.E., Planas, J.M. Population Pharmacokinetic Modeling of *trans*-Resveratrol and Its Glucuronide and Sulfate Conjugates After Oral and Intravenous Administration in Rats. *Pharm. Res.* 28 (7), 1606-1621, 2011.
- Corpet, D.E., Pierre, F. How good are rodent models of carcinogenesis in predicting efficacy in humans? A systematic review and meta-analysis of colon chemoprevention in rats, mice and men. *Eur. J. Cancer.* 41 (13), 1911-1922, 2005.
- Cottart, C.H., Nivet-Antoine, V., Laguillier-Morizot, C., Beaudeux, J.L. Resveratrol bioavailability and toxicity in humans. *Mol. Nutr. Food Res.* 54 (1), 7-16, 2010.
- Crowell, J.A., Korytko, P.J., Morrissey, R.L., Booth, T.D., Levine, B.S. Resveratrol-associated renal toxicity. *Toxicol. Sci.* 82 (2), 614-619, 2004.
- Csiszar, A., Labinskyy, N., Pinto, J.T., Ballabh, P., Zhang, H., Losonczy, G., et al. Resveratrol induces mitochondrial biogenesis in endothelial cells. *Am. J. Physiol. Heart Circ. Physiol.* 297 (1), H13-H20, 2009.
- Cui, X., Jin, Y., Hofseth, A.B., Pena, E., Habiger, J., Chumanovich, A., et al. Resveratrol suppresses colitis and colon cancer associated with colitis. *Cancer Prev. Res. (Phila.).* 3 (4), 549-559, 2010.
- Cummings, J.H., Bingham, S.A. Diet and the prevention of cancer. *BMJ.* 317 (7173), 1636-1640, 1998.
- Dal-Pan, A., Blanc, S., Aujard, F.** Resveratrol suppresses body mass gain in a seasonal non-human primate model of obesity. *BMC Physiol.* 10, 11, 2010.
- Das, D.K., Maulik, N. Resveratrol in cardioprotection: a therapeutic promise of alternative medicine. *Mol. Interv.* 6 (1), 36-47, 2006.
- Dawson, R.J., Locher, K.P. Structure of a bacterial multidrug ABC transporter. *Nature.* 443 (7108), 180-185, 2006.
- Dean, M. ABC transporters, drug resistance, and cancer stem cells. *J. Mammary Gland Biol. Neoplasia.* 14 (1), 3-9, 2009.

- Dean, M., Annilo, T. Evolution of the ATP-binding cassette (ABC) transporter superfamily in vertebrates. *Annu. Rev. Genomics Hum. Genet.* 6, 123-142, 2005.
- D'Haens, G.R. Top-down therapy for IBD: rationale and requisite evidence. *Nat. Rev. Gastroenterol. Hepatol.* 7 (2), 86-92, 2010.
- Diplock, A.T., Aggett, P.J., Ashwell, M., Bornet, F., Fern, E.B., Roberfroid, M.B. Scientific concepts of functional foods in Europe: Consensus Document. *Brit. J. Nutr.* 81 (4), S1-S27, 1999.
- Docherty, J.J., Fu, M.M., Stiffer, B.S., Limpero, R.J., Pokabla, C.M. DeLucia, A.L. Resveratrol inhibition of herpes simplex virus replication. *Antiviral Res.* 43 (3), 145-155, 1999.
- Druckrey, H., Preussmann, R., Matzkies, F., Ivankovic, S. Selective production of intestinal cancer in rats by 1,2-dimethylhydrazine. *Naturwissenschaften.* 54 (11), 285-286, 1967.
- E**I-Ferally, F. Isolation, characterization, and synthesis of 3,5,4'-trihydroxybibenzyl from Cannabis sativa. *J. Nat. Prod.* 47 (1), 89-92, 1984.
- Enokizono, J., Kusuhara, H., Sugiyama, Y. Regional expression and activity of breast cancer resistance protein (Bcrp/Abcg2) in mouse intestine: overlapping distribution with sulfotransferases. *Drug Metab. Dispos.* 35 (6), 922-928, 2007.
- F**an, P., Marston, A., Hay, A.E., Hostettmann, K. Rapid separation of three glucosylated resveratrol analogues from the invasive plant Polygonum cuspidatum by high-speed countercurrent chromatography. *J. Sep. Sci.* 32 (17), 2979-2984, 2009.
- Femia, A.P., Bendinelli, B., Giannini, A., Salvadori, M., Pinzani, P., Dolara, P., et al. Mucin-depleted foci have beta-catenin gene mutations, altered expression of its protein, and are dose- and time-dependent in the colon of 1,2-dimethylhydrazine-treated rats. *Int. J. Cancer.* 116 (1), 9-15, 2005.
- Femia, A.P., Dolara, P., Caderni, G. Mucin-depleted foci (MDF) in the colon of rats treated with azoxymethane (AOM) are useful biomarkers for colon carcinogenesis. *Carcinogenesis.* 25 (2), 277-281, 2004.
- Femia, A.P., Dolara, P., Giannini, A., Salvadori, M., Biggeri, A., Caderni, G. Frequent mutation of Apc gene in rat colon tumors and mucin-depleted foci, preneoplastic lesions in experimental colon carcinogenesis. *Cancer Res.* 67 (2), 445-449, 2007.
- Ferlay, J., Parkin, D.M., Steliarova-Foucher, E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur. J. Cancer.* 46 (4), 765-781, 2010.

- Fiala, E. Investigations into the metabolism and mode of action of the colon carcinogen 1, 2-dimethylhydrazine. *Cancer*. 36 (6 Suppl), 2407-2412, 1975.
- Filipe, M.I. Mucous secretion in rat colonic mucosa during carcinogenesis induced by dimethylhydrazine. A morphological and histochemical study. *Br. J. Cancer*. 32 (1), 60-77, 1975.
- Fischer-Posovszky, P., Kukulus, V., Tews, D., Unterkircher, T., Debatin, K.M., Fulda, S., et al. Resveratrol regulates human adipocyte number and function in a Sirt1-dependent manner. *Am. J. Clin. Nutr.* 92 (1), 5-15, 2010.
- Flores-Sanchez, I.J., Verpoorte, R. Secondary metabolism in cannabis. *Phytochem. Rev.* 7 (3), 615-639, 2008.
- Fodde, R., Kuipers, J., Rosenberg, C., Smits, R., Kielman, M., Gaspar, C., et al. Mutations in the APC tumour suppressor gene cause chromosomal instability. *Nat. Cell Biol.* 3 (4), 433-438, 2001.
- Frankel, E.N., Waterhouse, A.L., Kinsella, J.E. Inhibition of human LDL oxidation by resveratrol. *Lancet*. 341 (8852), 1103-1104, 1993.
- Frémont, L., Belguendouz, L., Delpal, S. Antioxidant activity of resveratrol and alcohol-free wine polyphenols related to LDL oxidation and polyunsaturated fatty acids. *Life. Sci.* 64 (26), 2511-2521, 1999.
- Fritzemeier, K.H., Kindl, H. 9,10-Dihydrophenanthrenes as phytoalexins of Orchidaceae. *Eur. J. Biochem.* 133 (3), 545- 550, 1983.
- Fromm, M.F. Importance of P-glycoprotein at blood-tissue barriers. *Trends Pharmacol. Sci.* 25 (8), 423-429, 2004.
- Fu, Z.D., Cao, Y., Wang, K.F., Xu, S.F., Han, R. Chemopreventive effect of resveratrol to cancer. *Ai Zheng.*, 23 (8), 869-873, 2004.
- Fulda, S., Debatin, K.M. Sensitization for tumor necrosis factor-related apoptosis-inducing ligand induced apoptosis by the chemopreventive agent resveratrol. *Cancer Res.*, 64 (1), 337-346, 2004.
- Gakh, A.A., Anisimova, N.Y., Kiselevsky, M.V., Sadovnikov, S.V., Stankov, I.N., Yudin, M.V., et al.** Dihydro-resveratrol--a potent dietary polyphenol. *Bioorg. Med. Chem. Lett.* 20 (20), 6149-6151, 2010.
- Garvin, S., Ollinger, K., Dabrosin, C. Resveratrol induces apoptosis and inhibits angiogenesis in human breast cancer xenografts in vivo. *Cancer Lett.*, 231 (1), 113-122, 2006.

- Gautam, R., Jachak, S.M. Recent developments in anti-inflammatory natural products. *Med. Res. Rev.* 29 (5), 767-820, 2009.
- Gehm, B.D., McAndrews, J.M., Chien, P.Y., Jameson, J.L. Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. *Proc. Natl. Acad. Sci., USA*, 94 (25), 14138-14143, 1997.
- Glauert, H.P., Bennink, M.R. Metabolism of 1,2-dimethylhydrazine by cultured rat colon epithelial cells. *Nutr. Cancer.* 5 (2), 78-86, 1983.
- González-Pons, E. Estudi del metabolisme intestinal i l'activitat sobre el sistema reproductor masculí del *trans*-resveratrol, un antioxidant natural del raïm. Tesi doctoral, 2005.
- Gorham, J. The biochemistry of the stilbenoids. 1^a ed. Regne Unit: Chapman & Hall; 1995.
- Gromadzińska, J., Wasowicz, W. The role of reactive oxygen species in the development of malignancies. *Int. J. Occup. Med. Environ. Health.* 13 (3), 233-245, 2000.
- Grønbaek, M. Wine and mortality. Evidence for causal inference? *Dan. Med. Bull.* 47 (4), 271-282, 2000.
- Gusman, J., Malonne, H., Atassi, G. A reappraisal of the potential chemopreventive and chemotherapeutic properties of resveratrol. *Carcinogenesis*, 22 (8), 1111-1117, 2001.
- Hall, M.D., Handley, M.D., Gottesman, M.M. Is resistance useless? Multidrug resistance and collateral sensitivity. *Trends Pharmacol. Sci.* 30 (10), 546-556, 2009.
- Halls, C., Yu, O. Potential for metabolic engineering of resveratrol biosynthesis. *Trends Biotechnol.* 26 (2), 77-81, 2008.
- Hambly, R.J., Rumney, C.J., Cunningham, M., Fletcher, J.M., Rijken, P.J., Rowland, I.R. Influence of diets containing high and low risk factors for colon cancer on early stages of carcinogenesis in human flora-associated (HFA) rats. *Carcinogenesis.* 18 (8), 1535-1539, 1997.
- Harikumar, K.B., Aggarwal, B.B. Resveratrol: a multitargeted agent for age-associated chronic diseases. *Cell Cycle.* 7 (8), 1020-1035, 2008.
- He, H., Lyons, K.A., Shen, X., Yao, Z., Bleasby, K., Chan, G., et al. Utility of unbound plasma drug levels and P-glycoprotein transport data in prediction of central nervous system exposure. *Xenobiotica.* 39 (9), 687-693, 2009.

- Hebbar, V., Shen, G., Hu, R., Kim, B.R., Chen, C., Korytko, P.J., et al. Toxicogenomics of resveratrol in rat liver. *Life Sci.* 76 (20), 2299-2314, 2005.
- Henry, C., Vitrac, X., Decendit, A., Ennamany, R., Krisa, S., Mérillon, J.M. Cellular uptake and efflux of *trans*-piceid and its aglycone *trans*-resveratrol on the apical membrane of human intestinal Caco-2 cells. *J. Agric. Food Chem.* 53 (3), 798-803, 2005.
- Hernández-Romero, Y., Rojas, J.I., Castillo, R., Rojas, A., Mata, R. Spasmolytic effects, mode of action, and structure-activity relationships of stilbenoids from Nidema boothii. *J. Nat. Prod.* 67 (2), 160-167, 2004.
- Hernández-Romero, Y., Acevedo, L., Sánchez, M. de L., Shier, W.T., Abbas, H.K., Mata, R. Phytotoxic activity of bibenzyl derivatives from the orchid Epidendrum rigidum. *J. Agric. Food Chem.* 53 (16), 6276-6280, 2005.
- Herron, D.C., Shank, R.C. DNA methylation during chronic administration of 1,2-dimethylhydrazine in a carcinogenic regimen. *Carcinogenesis.* 3 (8), 857-860, 1982.
- Hines, R.N., McCarver, D.G. The ontogeny of human drug-metabolizing enzymes: phase I oxidative enzymes. *J. Pharmacol. Exp. Ther.* 300 (2), 355-360, 2002.
- Ho, G.T., Moodie, F.M., Satsangi, J. Multidrug resistance 1 gene (P-glycoprotein 170): an important determinant in gastrointestinal disease? *Gut.* 52 (5), 759-766, 2003.
- Howitz, T.K., Bitterman, J.K., Cohen, H.Y., Lamming, D.W., Lavu, S., Wood, G.J., et al. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature*, 425 (6954), 191-196, 2003.
- Hung, C.W., Chen, Y.C., Hsieh, W.L., Chiou, S.H., Kao, C.L. Ageing and neurodegenerative diseases. *Ageing Res. Rev.* 9 (Suppl 1), S36-S46, 2010.
- Huls, M., Russel, F.G., Masereeuw, R. The role of ATP binding cassette transporters in tissue defense and organ regeneration. *J. Pharmacol. Exp. Ther.* 328 (1), 3-9, 2009.
- Jackson, P.E., Cooper, D.P., O'Connor, P.J., Povey, A.C. The relationship between 1,2-dimethylhydrazine dose and the induction of colon tumours: tumour development in female SWR mice does not require a K-ras mutational event. *Carcinogenesis.* 20 (3), 509-513, 1999.
- Jang, M.S., Cai, E.N., Udeani, G.O., Slowing, K.V., Thomas, C.F., Beecher, D.W.W., et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*, 275 (5297), 218-220, 1997.
- Jenab, M., Chen, J., Thompson, L.U. Sialomucin production in aberrant crypt foci relates to degree of dysplasia and rate of cell proliferation. *Cancer Lett.* 165 (1), 19-25, 2001.

- Jiang, H., Wood, K.V., Morgan, J.A. Metabolic engineering of the phenylpropanoid pathway in *Saccharomyces cerevisiae*. *Appl. Environ. Microbiol.* 71 (6), 2962-2969, 2005.
- Juan, M.E., Alfara, I., Planas, J.M. Determination of dihydroresveratrol in rat plasma by HPLC. *J. Agric. Food Chem.* 58 (12), 7472-7475, 2010.
- Juan, M.E., Buenafuente, J., Casals, I., Planas, J.M. Plasmatic levels of *trans*-resveratrol in rats. *Food Res. Int.* 35 (2-3), 195-199, 2002a.
- Juan, M.E., González-Pons, E., Munuera, T., Ballester, J., Rodríguez-Gil, J.E., Planas, J.M. *trans*-Resveratrol, a natural antioxidant from grapes, increases sperm output in healthy rats. *J. Nutr.* 135 (4), 757-760, 2005.
- Juan, M.E., González-Pons, E., Planas, J.M. Multidrug resistance proteins restrain the intestinal absorption of *trans*-resveratrol in rats. *J. Nutr.* 140 (3), 489-495, 2010a.
- Juan, M.E., Maijó, M., Planas, J.M. Quantification of *trans*-resveratrol and its metabolites in rat plasma and tissues by HPLC. *J. Pharm. Biomed. Anal.* 51 (2), 391-398, 2010b.
- Juan, M.E., Vinardell, M.P., Planas, J.M. The daily oral administration of high doses of *trans*-resveratrol to rats for 28 days is not harmful. *J. Nutr.* 132 (2), 257-260, 2002b.
- Juan, M.E., Wenzel, U., Daniel, H., Planas, J.M. Resveratrol induces apoptosis through ROS-dependent mitochondria pathway in HT-29 human colorectal carcinoma cells. *J. Agric. Food Chem.* 56 (12), 4813-4818, 2008.
- Jung, C.M., Heinze, T.M., Schnackenberg, L.K., Mullis, L.B., Elkins, S.A., Elkins, C.A., et al. Interaction of dietary resveratrol with animal-associated bacteria. *FEMS Microbiol. Lett.* 297 (2), 266-273, 2009.
- Kageura, T., Matsuda, H., Morikawa, T., Toguchida, I., Harima, S., Oda, M., et al. Inhibitors from rhubarb on lipopolysaccharide-induced nitric oxide production in macrophages: structural requirements of stilbenes for the activity. *Bioorg. Med. Chem.* 9 (7), 1887-1893, 2001.
- Kang, O.H., Jang, H.J., Chae, H.S., Oh, Y.C., Choi, J.G., Lee, Y.S., et al. Anti-inflammatory mechanisms of resveratrol in activated HMC-1 cells: pivotal roles of NF-kappaB and MAPK. *Pharmacol. Res.* 59 (5), 330-337, 2009.
- Kannan, P., John, C., Zoghbi, S.S., Halldin, C., Gottesman, M.M., Innis, R.B., et al. Imaging the function of P-glycoprotein with radiotracers: pharmacokinetics and in vivo applications. *Clin. Pharmacol. Ther.* 86 (4), 368-377, 2009.
- Kelly, G. A review of the sirtuin system, its clinical implications, and the potential role of dietary activators like resveratrol: part 1. *Altern. Med. Rev.* 15 (3), 245-263, 2010.

- Kensler, T., Guyton, K., Egner, P., McCarthy, T., Lesko, S., Akman, S. Role of reactive intermediates in tumor promotion and progression. *Prog. Clin. Biol. Res.* 391, 103-116, 1995.
- Khanduja, K.L., Bhardwaj, A. i Kaushik, G. Resveratrol inhibits N-nitrososdiethylamine-induced ornithine decarboxylase and cyclooxygenase in mice. *J. Nutr. Sci. Vitaminol. (Tokyo)*. 50 (1), 61-65, 2004.
- Kimura, Y., Okuda, H. Resveratrol isolated from *Polygonum cuspidatum* root prevents tumor growth and metastasis to lung and tumor-induced neovascularization in Lewis lung carcinoma-bearing mice. *J. Nutr.* 131 (6), 1844-1849, 2001.
- Kinzler, K.W., Vogelstein, B. Lessons from hereditary colorectal cancer. *Cell.* 87 (2), 159-170, 1996.
- Klaassen, C.D., Aleksunes, L.M. Xenobiotic, bile acid, and cholesterol transporters: function and regulation. *Pharmacol. Rev.* 62 (1), 1-96, 2010.
- Koboziev, I., Karlsson, F., Grisham, M.B. Gut-associated lymphoid tissue, T cell trafficking, and chronic intestinal inflammation. *Ann. N. Y. Acad. Sci.* 1207 (Suppl 1), E86-E93, 2010.
- Kodan, A., Kuroda, H., Sakai, F. A stilbene synthase from Japanese red pine (*Pinus densiflora*): implications for phytoalexin accumulation and down-regulation of flavonoid biosynthesis. *Proc. Natl. Acad. Sci. U.S.A.* 99 (5), 3335-3339, 2002.
- Kong, H., Kim, Y., Lee, Y., Choi, B. Sulfate-conjugated methylprednisolone: Evaluation as a colon-specific methylprednisolone prodrug and comparison with sulfate-conjugated prednisolone and dexamethasone. *J. Drug Target.* 17 (2), 159-167, 2009.
- Lampe, J.W., Chang, J.L. Interindividual differences in phytochemical metabolism and disposition. *Semin. Cancer Biol.* 17 (5), 347-353, 2007.
- Larrosa, M., Yañéz-Gascón, M.J., Selma, M.V., González-Sarrías, A., Toti, S., Cerón, J.J., et al. Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model. *J. Agric. Food Chem.* 57 (6), 2211-2220, 2009.
- de la Lastra, C.A., Villegas, I. Resveratrol as an anti-inflammatory and anti-aging agent: mechanisms and clinical implications. *Mol. Nutr. Food Res.* 49 (5), 405-430, 2005.
- Levsen, K., Schiebel, H.M., Behnke, B., Dötzer, R., Dreher, W., Elend, M., et al. Structure elucidation of phase II metabolites by tandem mass spectrometry: an overview. *J. Chromatogr. A.* 1067 (1-2), 55-72, 2005.

Li, Z.G., Hong, T., Shimada, Y., Komoto, I., Kawabe, A., Ding, Y. Suppression of N-nitrosomethylbenzylamine (NMBA)-induced esophageal tumorigenesis in F344 rats by resveratrol. *Carcinogenesis*. 23 (9), 1531-1536, 2002.

Lin, K.H., Hsiao, G., Shih, C.M., Chou, D.S., Sheu, J.R. Mechanisms of resveratrol-induced platelet apoptosis. *Cardiovasc Res*. 83 (3), 575-585, 2009.

Locher, K.P. Review. Structure and mechanism of ATP-binding cassette transporters. *Phil. Trans. R. Soc. B*. 364 (1514), 239-245, 2009.

Maier-Salamon, A., Böhmdorfer, M., Reznicek, G., Thalhammer, T., Szekeres, T., Jaeger, W. Hepatic Glucuronidation of Resveratrol: Interspecies Comparison of Enzyme Kinetic Profiles in Human, Mouse, Rat and Dog. *Drug Metab. Pharmacokinet.* 2011. doi:10.2133/dmpk.DMPK-11-RG-006.

Maier-Salamon, A., Hagenauer, B., Reznicek, G., Szekeres, T., Thalhammer, T., Jäger, W. Metabolism and disposition of resveratrol in the isolated perfused rat liver: role of Mrp2 in the biliary excretion of glucuronides. *J. Pharm. Sci.* 97 (4), 1615-1628, 2008.

Maier-Salamon, A., Hagenauer, B., Wirth, M., Gabor, F., Szekeres, T., Jäger, W. Increased transport of resveratrol across monolayers of the human intestinal Caco-2 cells is mediated by inhibition and saturation of metabolites. *Pharm. Res.* 23 (9), 2107-2115, 2006.

Marier, J.F., Vachon, P., Gritsas, A., Zhang, J., Moreau, J.P., Ducharme, M.P. Metabolism and disposition of resveratrol in rats: extent of absorption, glucuronidation, and enterohepatic recirculation evidenced by a linked-rat model. *J. Pharmacol. Exp. Ther.* 302 (1), 369-373, 2002.

Martín, A.R., Villegas, I., Sánchez-Hidalgo, M., de la Lastra, C.A. The effects of resveratrol, a phytoalexin derived from red wines, on chronic inflammation induced in an experimentally induced colitis model. *Br. J. Pharmacol.* 147 (8), 873-885, 2006.

Martinez, M. E., O'Brien, T.G., Fultz, K.E., Babbar, N., Yerushalmi, H., Qu, N., et al. Pronounced reduction in adenoma recurrence associated with aspirin use and a polymorphism in the ornithine decarboxylase gene. *Proc. Natl Acad. Sci. USA.* 100 (13), 7859-7864, 2003.

Maskens, A.F. Confirmation of the two-step nature of chemical carcinogenesis in the rat colon adenocarcinoma model. *Cancer Res.* 41 (3), 1240-1245, 1981.

McConnell, E.L., Fadda, H.M., Basit, A.W. Gut instincts: explorations in intestinal physiology and drug delivery. *Int. J. Pharm.* 364 (2), 213-226, 2008.

McLellan, E.A., Medline, A., Bird, R.P. Sequential analysis of the growth and morphological characteristics of aberrant crypt foci: putative preneoplastic lesions. *Cancer Res.* 51 (19), 5270-5274, 1991.

Miller, R.A., Harrison, D.E., Astle, C.M., Baur, J.A., Boyd, A.R., de Cabo, R., et al. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *J. Gerontol. A Biol. Sci. Med. Sci.* 66 (2), 191-201, 2011.

Muntané, J. Regulation of drug metabolism and transporters. *Curr. Drug Metab.* 10 (8), 932-945, 2009.

Murakami, T., Takano, M. Intestinal efflux transporters and drug absorption. *Expert Opin. Drug Metab. Toxicol.* 4 (7), 923-939, 2008.

Nakagama, H., Nakanishi, M., Ochiai, M. Modeling human colon cancer in rodents using a food-borne carcinogen, PhIP. *Cancer Sci.* 96 (10), 627-636, 2005.

Nakamura, T., Yamamori, M., Sakaeda, T. Pharmacogenetics of intestinal absorption. *Curr. Drug Deliv.* 5 (3), 153-169, 2008.

Namasivayam, N. Chemoprevention in experimental animals. *Ann. N. Y. Acad. Sci.* 1215, 60-71, 2011.

Narayan, S., Roy, D. Role of APC and DNA mismatch repair genes in the development of colorectal cancers. *Mol. Cancer.* 2, 41, 2003.

Ohnishi, N., Yokoyama, T. Interactions between medicines and functional foods or dietary supplements. *Keio J. Med.* 53 (3), 137-150, 2004.

Orsini, F., Verotta, L., Lecchi, M., Restano, R., Curia, G., Redaelli, E., et al. Resveratrol derivatives and their role as potassium channels modulators. *J. Nat. Prod.* 67 (3), 421-426, 2004.

Ortuño, J., Covas, M.I., Farre, M., Pujadas, M., Fito, M., Khymenets, O., et al. Matrix effects on the bioavailability of resveratrol in humans. *Food Chem.* 120 (4), 1123-1130, 2010.

Oshima, M., Dinchuk, J.E., Kargman, S.L., Oshima, H., Hancock, B., Kwong, E., et al. Suppression of intestinal polyposis in Apc delta716 knockout mice by inhibition of cyclooxygenase 2 (COX-2). *Cell.* 87 (5), 803-809, 1996.

Pacholec, M., Bleasdale, J.E., Chrunky, B., Cunningham, D., Flynn, D., Garofalo, R.S., et al. SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1. *J. Biol. Chem.* 285 (11), 8340-8351, 2010.

- Pallàs, M., Casadesús, G., Smith, M.A., Coto-Montes, A., Pelegri, C., Vilaplana, J., et al. Resveratrol and neurodegenerative diseases: activation of SIRT1 as the potential pathway towards neuroprotection. *Curr. Neurovasc. Res.* 6 (1), 70-81, 2009.
- Pang, K.S., Maeng, H.J., Fan, J. Interplay of transporters and enzymes in drug and metabolite processing. *Mol. Pharm.* 6 (6), 1734-1755, 2009.
- Panwala, C.M., Jones, J.C., Viney, J.L. A novel model of inflammatory bowel disease: mice deficient for the multiple drug resistance gene, mdr1a, spontaneously develop colitis. *J. Immunol.* 161 (10), 5733-5744, 1998.
- Patel, K.R., Brown, V.A., Jones, D.J., Britton, R.G., Hemingway, D., Miller, A.S., et al. Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. *Cancer Res.* 70 (19), 7392-7399, 2010.
- Paul, B., Masih, I., Deopujari, J., Charpentier, C. Occurrence of resveratrol and pterostilbene in age-old darakchasava, an ayurvedic medicine from India. *J. Ethnopharmacol.* 68 (1-3), 71-76, 1999.
- Pedras, M.S., Ahiahonu, P.W. Metabolism and detoxification of phytoalexins and analogs by phytopathogenic fungi. *Phytochemistry.* 66 (4), 391-411, 2005.
- Penumathsa, S.V., Maulik, N. Resveratrol: a promising agent in promoting cardioprotection against coronary heart disease. *Can. J. Physiol. Pharmacol.* 87 (4), 275-286, 2009.
- Pervaiz, S., Holme, A.L. Resveratrol: its biologic targets and functional activity. *Antioxid. Redox Signal.* 11 (11), 2851-2897, 2009.
- Pierre, F., Freeman, A., Taché, S., Van der Meer, R., Corpet, D.E. Beef meat and blood sausage promote the formation of azoxymethane-induced mucin-depleted foci and aberrant crypt foci in rat colons. *J. Nutr.* 134 (10), 2711-2716, 2004.
- Pretlow, T.P., Barrow, B.J., Ashton, W.S., O'Riordan, M.A., Pretlow, T.G., Jurcisek, J.A., et al. Aberrant crypts: putative preneoplastic foci in human colonic mucosa. *Cancer Res.* 51 (5), 1564-1567, 1991.
- Procko, E., O'Mara, M.L., Bennett, W.F., Tielemans, D.P., Gaudet, R. The mechanism of ABC transporters: general lessons from structural and functional studies of an antigenic peptide transporter. *FASEB J.* 23 (5), 1287-1302, 2009.
- Raju, J., Bird, R.P. Energy restriction reduces the number of advanced aberrant crypt foci and attenuates the expression of colonic transforming growth factor β and

cyclooxygenase isoforms in zucker obese (fa/fa) rats. *Cancer Res.* 63 (20), 6595-6601, 2003.

Rao, C.V., Wang, C., Simi, B., Lubet, R.A., Kelloff, G.J., Steele, V., et al. Enhancement of experimental colon cancer by genistein. *Cancer Res.* 57 (17), 3717-3722, 1997.

Reagan-Shaw, S., Afaq, F., Aziz, M.H., Ahmad, N. Modulations of critical cell cycle regulatory events during chemoprevention of ultraviolet B-mediated responses by resveratrol in SKH-1 hairless mouse skin. *Oncogene*, 23 (30), 5151-5160, 2004.

Reddy, B.S. Studies with the azoxymethane-rat preclinical model for assessing colon tumor development and chemoprevention. *Environ. Mol. Mutagen.* 44 (1), 26-35, 2004.

Renaud, S., de Lorgeril, M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet.* 339 (8808), 1523-1526, 1992.

Renaud, S.C., Guéguen, R., Siest, G., Salamon, R. Wine, beer, and mortality in middle-aged men from eastern France. *Arch. Intern. Med.* 159 (16), 1865-1870, 1999.

Resta-Lenert, S., Smitham, J., Barrett, K.E. Epithelial dysfunction associated with the development of colitis in conventionally housed mdr1a^{-/-} mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* 289 (1), G153-G162, 2005.

Revel, A., Haimov-Kochman, R., Porat, A., Lewin, A., Simon, A., Laufer, N., et al. In vitro fertilization-intracytoplasmic sperm injection success rates with cryopreserved sperm from patients with malignant disease. *Fertil. Steril.* 84 (1), 118-122, 2005.

Roberfroid, M.B. Global view on functional foods: European perspectives. *Br. J. Nutr.* 88 (Suppl 2), S133-138, 2002.

Roberts, D.M., Buckley, N.A. Pharmacokinetic considerations in clinical toxicology: clinical applications. *Clin. Pharmacokinet.* 46 (11), 897-939, 2007.

Robey, R.W., To, K.K., Polgar, O., Dohse, M., Fetsch, P., Dean, M., et al. ABCG2: a perspective. *Adv. Drug Deliv. Rev.* 61 (1), 3-13, 2009.

Rodrigues, M.A.M., Silva, L.A.G., Salvadori, D.M.F., de Camargo, J.L.V. i Montenegro, M.R. Aberrant crypt foci and colon cancer: comparison between a short- and medium-term bioassay for colon carcinogenesis using dimethylhydrazine in Wistar rats. *Braz. J. Med. Biol. Res.* 35 (3), 251-355, 2002.

Sabolovic, N., Humbert, A.C., Radominska-Pandya, A., Magdalou, J. Resveratrol is efficiently glucuronidated by UDP-glucuronosyltransferases in the human gastrointestinal tract and in Caco-2 cells. *Biopharm. Drug Dispos.* 27 (4), 181-189, 2006.

- Sakamoto, H., Yokota, H., Kibe, R., Sayama, Y., Yuasa, A. Excretion of bisphenol A-glucuronide into the small intestine and deconjugation in the cecum of the rat. *Biochim. Biophys. Acta.* 1573 (2), 171-176, 2002.
- Sale, S., Verschoyle, R.D., Boocock, D., Jones, D.J., Wilsher, N., Ruparelia, K.C., et al. Pharmacokinetics in mice and growth-inhibitory properties of the putative cancer chemopreventive agent resveratrol and the synthetic analogue trans 3,4,5,4'-tetramethoxystilbene. *Br. J. Cancer.* 90 (3), 736-744, 2004.
- Sánchez-Fidalgo, S., Cárdeno, A., Villegas, I., Talero, E., de la Lastra, C.A. Dietary supplementation of resveratrol attenuates chronic colonic inflammation in mice. *Eur. J. Pharmacol.* 633 (1-3), 78-84, 2010.
- Schinkel, A.H., Mol, C.A., Wagenaar, E., van Deemter, L., Smit, J.J., Borst, P. Multidrug resistance and the role of P-glycoprotein knockout mice. *Eur. J. Cancer.* 31A (7-8), 1295-1298, 1995.
- Sengottuvelan, M., Viswanathan, P., Nalini, N. Chemopreventive effect of *trans*-resveratrol--a phytoalexin against colonic aberrant crypt foci and cell proliferation in 1,2-dimethylhydrazine induced colon carcinogenesis. *Carcinogenesis.* 27 (5), 1038-1046, 2006.
- Sargent, T., Ribonnet, L., Kolosova, A., Garsou, S., Schaut, A., De Saeger, S., et al. Molecular and cellular effects of food contaminants and secondary plant components and their plausible interactions at the intestinal level. *Food Chem. Toxicol.* 46 (3), 813-841, 2008.
- Shukla, Y., Singh, R. Resveratrol and cellular mechanisms of cancer prevention. *Ann. N. Y. Acad. Sci.* 1215, 1-8, 2011.
- Siemann, E.H., Creasy, L.L. Concentration of the phytoalexin resveratrol in wine. *Am. J. Enol. Vitic.* 43 (1), 41-52, 1992.
- Singh, U.P., Singh, N.P., Singh, B., Hofseth, L.J., Price, R.L., Nagarkatti, M., et al. Resveratrol (*trans*-3,5,4'-trihydroxystilbene) induces silent mating type information regulation-1 and down-regulates nuclear transcription factor-kappaB activation to abrogate dextran sulfate sodium-induced colitis. *J. Pharmacol. Exp. Ther.* 332 (3), 829-839, 2010.
- Sohn, K.J., Puchyr, M., Salomon, R.N., Graeme-Cook, F., Fung, L., Choi, S.W., et al. The effect of dietary folate on Apc and p53 mutations in the dimethylhydrazine rat model of colorectal cancer. *Carcinogenesis.* 20 (12), 2345-2350, 1999.

- Soleas, G.J., Diamandis, E.P., Goldberg, D.M. Resveratrol: a molecule whose time has come? And gone? *Clin. Biochem.* 30 (2), 91-113, 1997.
- Stanley, L.A., Horsburgh, B.C., Ross, J., Scheer, N., Wolf, C.R. Drug transporters: gatekeepers controlling access of xenobiotics to the cellular interior. *Drug Metab. Rev.* 41 (1), 27-65, 2009.
- Subbaramaiah, K. Chung, W.J., Michaluart, P., Telang, N., Tanabe, T., Inoue, H., et al. Resveratrol inhibits cyclooxygenase-2 transcription and activity in phorbol ester-treated human mammary epithelial cells. *J. Biol. Chem.*, 273 (34), 21875-21882, 1998.
- Suh, N., Paul, S., Hao, X., Simi, B., Xiao, H., Rimando, A.M., et al. Pterostilbene, an active constituent of blueberries, suppresses aberrant crypt foci formation in the azoxymethane-induced colon carcinogenesis model in rats. *Clin. Cancer Res.* 13 (1), 350-355, 2007.
- Sugimura, T., Terada, M., Yokota, J., Hirohashi, S., Wakabayashi, K. Multiple genetic alterations in human carcinogenesis. *Environ. Health Perspect.* 98, 5-12, 1992.
- Sun, A.Y., Wang, Q., Simonyi, A., Sun, G.Y. Resveratrol as a therapeutic agent for neurodegenerative diseases. *Mol. Neurobiol.* 41 (2-3), 375-383, 2010.
- Szkudelski, T. Resveratrol-induced inhibition of insulin secretion from rat pancreatic islets: evidence for pivotal role of metabolic disturbances. *Am. J. Physiol. Endocrinol. Metab.* 293 (4), E901-E907, 2007.
- T**adolini, B., Juliano, C., Piu, L., Franconi, F., Cabrini, L. Resveratrol inhibition of lipid peroxidation. *Free Radic. Res.* 33 (1), 105-114, 2000.
- Takahashi, M., Mutoh, M., Kawamori, T., Sugimura, T., Wakabayashi, K. Altered expression of beta-catenin, inducible nitric oxide synthase and cyclooxygenase-2 in azoxymethane-induced rat colon carcinogenesis. *Carcinogenesis.* 21 (7), 1319-1327, 2000.
- Tanaka, Y., Slitt, A.L., Leazer, T.M., Maher, J.M., Klaassen, C.D. Tissue distribution and hormonal regulation of the breast cancer resistance protein (Bcrp/Abcg2) in rats and mice. *Biochem. Biophys. Res. Commun.* 326 (1), 181-187, 2005.
- Tessitore, L., Davit, A., Sarotto, I., Caderni, G. Resveratrol depresses the growth of colorectal aberrant crypt foci by affecting bax and p21(CIP) expression. *Carcinogenesis.* 21 (8), 1619-1622, 2000.
- Thelen, K., Dressman, J.B. Cytochrome P450-mediated metabolism in the human gut wall. *J. Pharm. Pharmacol.* 61 (5), 541-558, 2009.

Tseng, S.H., Lin, S.M., Chen, J.C., Su, Y.H., Huang, H.Y., Chen, C.K., et al. Resveratrol suppresses the angiogenesis and tumor growth of gliomas in rats. *Clin. Cancer Res.* 10 (6), 2190-2202, 2004.

Ugurlalp, S., Usta, U., Mizrak, B. Resveratrol may reduce apoptosis of rat testicular germ cells after experimental testicular torsion. *Eur. J. Pediatr. Surg.* 15 (5), 333-336, 2005.

Van de Wetering, K., Burkon, A., Feddema, W., Bot, A., de Jonge, H., Somoza, V., et al. Intestinal breast cancer resistance protein (BCRP)/Bcrp1 and multidrug resistance protein 3 (MRP3)/Mrp3 are involved in the pharmacokinetics of resveratrol. *Mol. Pharmacol.* 75 (4), 876-885, 2009.

Van Herwaarden, A.E., Jonker, J.W., Wagenaar, E., Brinkhuis, R.F., Schellens, J.H., Beijnen, J.H., et al. The breast cancer resistance protein (Bcrp1/Abcg2) restricts exposure to the dietary carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine. *Cancer Res.* 63 (19), 6447-6452, 2003.

Vastano, B.C., Chen, Y., Zhu, N., Ho, C.T., Zhou, Z., Rosen, R.T. Isolation and identification of stilbenes in two varieties of *Polygonum cuspidatum*. *J. Agric. Food Chem.* 48 (2), 253-256, 2000.

Verghese, M., Rao, D.R., Chawan, C.B., Williams, L.L., Shackelford, L. Dietary inulin suppresses azoxymethane-induced aberrant crypt foci and colon tumours at the promotion stage in young Fisher 344 rats. *J. Nutr.* 132 (9), 2809-2813, 2002.

Vitrac, X., Desmoulière, A., Brouillaud, B., Krisa, S., Deffieux, G., Barthe, N., et al. Distribution of [¹⁴C]-*trans*-resveratrol, a cancer chemopreventive polyphenol, in mouse tissues after oral administration. *Life Sci.* 72 (20), 2219-2233, 2003.

Vivona, A.A., Shpitz, B., Medline, A., Bruce, W.R., Hay, K., Ward, M.A., et al. K-ras mutations in aberrant crypt foci, adenomas and adenocarcinomas during azoxymethane-induced colon carcinogenesis. *Carcinogenesis.* 14 (9), 1777-1781, 1993.

Vlaming, M.L., Lagas, J.S., Schinkel, A.H. Physiological and pharmacological roles of ABCG2 (BCRP): recent findings in Abcg2 knockout mice. *Adv. Drug Deliv. Rev.* 61 (1), 14-25, 2009.

Vrhovsek, U., Wendelin, S., Eder, R. Effects of Various Vinification Techniques on the Concentration of *cis*- and *trans*-Resveratrol and Resveratrol Glucoside Isomers in Wine. *Am. J. Enol. Vitic.* 48 (2), 214-219, 1997.

Walle, T. Bioavailability of resveratrol. *Ann. N. Y. Acad. Sci.* 1215, 9-15, 2011.

- Walle, T., Hsieh, F., DeLegge, M.H., Oatis, J.E. Jr., Walle, U.K. High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab. Dispos.* 32 (12), 1377-1382, 2004.
- Wang, Q., Xu, J., Rottinghaus, G.E., Simonyi, A., Lubahn, D., Sun, G.Y., et al. Resveratrol protects against global cerebral ischemic injury in gerbils. *Brain Res.* 958 (2), 439-447, 2002.
- Wang, D., Hang, T., Wu, C., Liu, W. Identification of the major metabolites of resveratrol in rat urine by HPLC-MS/MS. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 829 (1-2), 97-106, 2005.
- Wargovich, M.J., Jimenez, A., McKee, K., Steele, V.E., Velasco, M., Woods, J., et al. Efficacy of potential chemopreventive agents on rat colon aberrant crypt formation and progression. *Carcinogenesis.* 21 (6), 1149-1155, 2000.
- Watson, A.J. An overview of apoptosis and the prevention of colorectal cancer. *Crit. Rev. Oncol. Hematol.* 57 (2), 107-121, 2006.
- Wells, H.G., Slye, M., Holmes, H.F. Comparative pathology of cancer of the alimentary canal, with report of cases in mice. *Am. J. Cancer.* 33, 223-238, 1938.
- Westphal, C.H., Dipp, M.A., Guarente, L. A therapeutic role for sirtuins in diseases of aging? *Trends Biochem. Sci.* 32 (12), 555-560, 2007.
- Wilk, J.N., Bilsborough, J., Viney, J.L. The mdr1a^{-/-} mouse model of spontaneous colitis: a relevant and appropriate animal model to study inflammatory bowel disease. *Immunol. Res.* 31 (2), 151-159, 2005.
- Williams, D., Verghese, M., Walker, L.T., Boateng, J., Shackelford, L., Chawan, C.B. Flax seed oil and flax seed meal reduce the formation of aberrant crypt foci (ACF) in azoxymethane-induced colon cancer in Fisher 344 male rats. *Food Chem. Toxicol.* 45 (1), 153-159, 2007.
- Wulff, H., Castle, N.A., Pardo, L.A. Voltage-gated potassium channels as therapeutic targets. *Nat. Rev. Drug Discov.* 8 (12), 982-1001, 2009.
- Xavier, R.J., Podolsky, D.K. Unravelling the pathogenesis of inflammatory bowel disease. *Nature.* 448 (7152), 427-434, 2007.
- Xiao, K., Zhang, H.J., Xuan, L.J., Zhang, J., Xu, Y.M., Bai, D.L. Stilbenoids: chemistry and bioactivities. A: Atta-ur-Rahman, F.R.S., editor. Studies in natural products chemistry. Regne Unit: Elsevier; 2008. p. 453-646.

- Xie, C.F., Yuan, H.Q., Qu, J.B., Xing, J., Lü, B.B., Wang, X.N., et al. Biocatalytic production of acyclic bis[bibenzyls] from dihydroresveratrol by crude *Momordica charantia* peroxidase. *Chem. Biodivers.* 6 (8), 1193-1201, 2009.
- Xing, Y., Clements, W.K., Kimelman, D., Xu, W. Crystal structure of a beta-catenin/axin complex suggests a mechanism for the beta-catenin destruction complex. *Genes Dev.* 17 (22), 2753-2764, 2003.
- Y**ao, J., Wang, J.Y., Liu, L., Li, Y.X., Xun, A.Y., Zeng, W.S., et al. Anti-oxidant effects of resveratrol on mice with DSS-induced ulcerative colitis. *Arch. Med. Res.* 41 (4), 288-294, 2010.
- Yoshimi, N., Morioka, T., Kinjo, T., Inamine, M., Kaneshiro, T., Shimizu, T., et al. Histological and immunohistochemical observations of mucin-depleted foci (MDF) stained with alcian blue, in rat colon carcinogenesis induced with 1,2-dimethylhydrazine dihydrochloride. *Cancer Sci.* 95 (10), 792-797, 2004.
- Youn, J., Lee, J.S., Na, H.K., Kundu, J.K., Surh, Y.J. Resveratrol and piceatannol inhibit iNOS expression and NF-kappaB activation in dextran sulfate sodium-induced mouse colitis. *Nutr. Cancer.* 61 (6), 847-854, 2009.
- Yu, L., Sun, Z.J., Wu, S.L., Pan, C.E. Effect of resveratrol on cell cycle proteins in murine transplantable liver cancer. *World J. Gastroenterol.* 9 (10), 2341-2343, 2003.
- Z**amek-Gliszczynski, M.J., Nezasa, K., Tian, X., Kalvass, J.C., Patel, N.J., Raub, T.J., et al. The important role of Bcrp (Abcg2) in the biliary excretion of sulfate and glucuronide metabolites of acetaminophen, 4-methylumbelliflferone, and harmol in mice. *Mol. Pharmacol.* 70 (6), 2127-2133, 2006.
- Zheng, Y., Kramer, P.M., Lubet, R.A., Steele, V.E., Kelloff, G.J., Pereira, M.A. Effect of retinoids on AOM-induced colon cancer in rats: modulation of cell proliferation, apoptosis and aberrant crypt foci. *Carcinogenesis.* 20 (2), 255-260, 1999.
- Zhou, H.B., Chen, J.J., Wang, W.X., Cai, J.T., Du, Q. Anticancer activity of resveratrol on implanted human primary gastric carcinoma cells in nude mice. *World J. Gastroenterol.*, 11 (2), 280-284, 2005.