Journal of Microbiology, Biotechnology and Food Sciences

Baková et al. 2012 : 1 (February Special issue) 583-592

A REVIEW

INTRACELLULAR MECHANISMS OF NATURAL SUBSTANCES INVOLVED IN THE REGULATION OF CELL SURVIVAL AND APOPTOSIS: A REVIEW

Zuzana Baková[*1], Nora Maruniaková[1], Sushmita Nath[2], Adriana Kolesárová[1]*

Address: [1]Slovak University of Agriculture in Nitra, Faculty of Biotechnology and and Food Science, Department of Animal Physiology, Tr. A. Hlinku 2, 949 76 Nitra, Slovak Republic
[2]Sushmita Nath, M.Sc. Life Science (Zoology); PGDBI, Assam University: Silchar, Ethnobotany and Medicinal Plant Research Laboratory, Department of Life Science and Bioinformatics, 788011 Silchar, India

*Corresponding author: Zuzana.Bakova@yahoo.com

ABSTRACT

Natural substances which are considered to be a food or part of a food that provides medical and health benefits are called nutraceuticals. Resveratrol is one of such substances that signify potential benefit as anti-carcinogenic, lowering of blood sugar level, anti-inflammatory, antioxidant and cardioprotective properties in various types of cells and animal models including inhibition of PI3K/AKT/mTOR pathway. Activation of PI3K/Akt/mTOR pathway plays a pivotal role in essential cellular functions such as survival, proliferation, migration and differentiation in various types of cells. As the *in vivo* functions of mTOR remain elusive is possible that mTOR plays more important roles than had been anticipated from studies.

Keywords: natural substances, mTOR pathway, resveratrol

INTRODUCTION

The relationship between nutrition and physiological processes has been the aim of interest to physiologists since the end of the 19th century **(Heape, 1899; Marshall, 1904)**. In recent years considerable effort has been made to identify the metabolic and nutritional factors linking nutrition with partial physiological processes **(Monget and Martin, 1997; Kolesárová *et al.*, 2011)**.

Nowadays, the study of natural substances with pharmacological activity, such as flavonoids, has become an emerging trend in nutritional and pharmacologic research. Numerous data from various mammalian species have shown that nutrition may influence the physiological functions including the reproductive efficiency **(Prunier and Quesnel, 2000)**, tumorigenesis **(Subash *et al.*, 2010)**, carcinogenesis, angiogenesis, cell survival, proliferation and invasion **(Subash *et al.*, 2010; Aggarwal *et al.*, 2009)**. Natural substances which are considered to be a food or part of a food that provides medical and health benefits are called nutraceuticals (a term formed by combining the words "nutrition" and "pharmaceutical") **(Brower, 1998; Zeisel, 1999)**.

Most experimental studies involving farm animals have focussed on the negative consequences of undernutrition on reproductive performance **(Prunier and Quesnel, 2000)**. Ovarian activity, growth of antral follicles, ovulation rate, delay of puberty and returning to oestrus after weaning in farm animals is influenced by nutrition and body reserves **(Downing and Scaramuzzi, 1991; Prunier and Quesnel, 2000)**.

Oocyte maturation and hence the number of viable embryos per litter can be also effected by nutrition. Plant phenolics presented in fruit and vegetables and particularly in red wine, have received considerable attention because of their potential antioxidant **(López-Vélez*et al.*, 2003)**, anti-carcinogenic **(Wang *et al,* 2003; Jiang *et al.*, 2005)**, anti-inflammatory **(Liu *et al.*, 2010)** and cardioprotective activity **(Soleas *et al.*, 2006)**.

Multiple apoptotic signaling cascades may be activated by naturally ocurring flavonoids, including resveratrol, from which Phosphatidylinositol 3-kinases/Akt protein kinase/ Mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway is an important signaling cascade involved in the regulation of cell growth and proliferation in a various types of cells **(Teiten *et al.*, 2010; Brito *et al.*, 2009)**.

Resveratrol

Resveratrol (trans-3,5,4'-trihydroxystilbene) (Fig 1) is a naturally occuring polyphenol structurally related to stilbenes **(Rocha-Gonzáles *et al*., 2008)** synthesized by plants as a phytoalexin that protects against ultraviolet radiation and fungal infection **(Mukherjee *et al*., 2010; Jiang *et al*., 2005)**. Resveratrol occurs in two isoforms *cis*- and *trans*- resveratrol, but *trans*- resveratrol is more biologically active than its *cis* isoform **(Mukherjee *et al*., 2010)**. It is found in high concentration in natural foods such as grapes, mulberry, lingberry, bilberry, nuts, blueberries, red grapes, wine **(Das and Maulik, 2006)** and by at least 72 medicinal and edible plant species in response to stress conditions **(Rocha-Gonzáles *et al*., 2008)**.

The fact that resveratrol is contained in a wide variety of dietary resources gives a reason to think that regular consumption of resveratrol in the diet may be useful for treatment of multiple illnesses in which it has shown pharmacological activity **(Rocha-Gonzáles *et al*., 2008)**. Resveratrol signify potentially beneficial anti-carcinogenic **(Athar *et al*., 2009; Shankar *et al*., 2007ab; Polans, 2007; Jiang *et al*., 2007; Aggarwal, 2010)**, blood-sugar-lowering **(Mukherjee *et al*., 2010)**, cardioprotective **(Das and Maulik, 2006)**, anti-inflammatory **(Jiang *et al*., 2005)**, chemoprotective **(Shankar *et al*., 2007ab; Slusarz *et al*., 2010; Wu *et al*., 2010; Bai *et al*., 2010; Harikumar *et al*, 2010;Lee *et al*., 2009; Li *et al*., 2009)** and antioxidant **(Hattori *et al*., 2002)** activities in various types of cells and animal models. Most likely the *in vivo* antioxidant property of resveratrol is derived from its ability to increase nitric oxide (NO) synthesis, which in turns acts as an antioxidant. It has been shown that resveratrol induces NO synthesis in case of ischemic reperfused heart, brain and kidney and lower the oxidative stress **(Hattori *et al*., 2002; Cadenas and Barja, 1999)**. Resveratrol has also been shown to exhibit profound *in vitro* and *in vivo* growth-inhibitory and apoptosis-inducing activities in several cancer cell lines and animal models of carcinogenesis and tumorigenesis **(Joe *et al*., 2002; Jiang *et al*., 2007)**. These properties have been linked to the inhibition of proliferation in association with cell cycle arrest and apoptotic cell death typically observed *in vitro* **(Joe *et al*., 2002; Sun *et al*., 2006; Van Ginkel *et al*., 2010; Jiang *et al*., 2005)**. In addition, resveratrol also exerts its effects by interacting with multiple cellular targets and modulating various signal transduction pathways **(Athar *et al*., 2009)**. To further examine the effect of resveratrol on mammalian target of rapamycin (mTOR) human U251 glioma cells were treated with resveratrol. The results suggest that resveratrol decreases the activation of Akt/mTOR and inhibition of mTOR by rapamycin further enhances the resveratrol-induced apoptosis **(Jiang *et al*., 2005)**. Other authors suggest that resveratrol is

able to inhibit PI3K/Akt/mTOR pathway in various types of cells **(Shankar *et al.*, 2007ab; Bai *et al.*, 2010; Srivastava *et al.*, 2010)**.

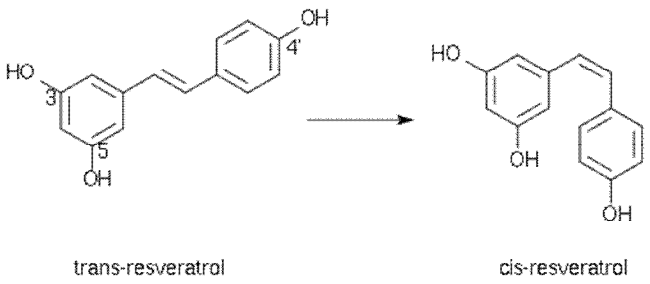

Figure 1 Isoforms *trans*-resveratol and *cis*-resveratrol **(Melzoch *et al.*, 2000)**

mTOR signaling pathway

The hormonal control of particular physiological processes uses a number of distinct and sometimes interconnected signaling pathways **(Kesari *et al.*, 2005; Bjornsti and Houghton, 2004)**. In mammalian cells, mTOR is a large polypeptide kinase that acts as a nutrient sensor and regulator of translation **(Schmelzle and Hall, 2000; Kesari *et al.*, 2005; Bjornsti and Houghton, 2004; Dutcher, 2004; Fingar *et al.* 2004)** and proliferation by controlling cell growth or acting directly on the phosphorylation cascade that controls cell cycle regulatory proteins **(Fingar *et al.* 2004)**. Activation of PI3K/Akt/mTOR pathway plays a pivotal role in essential cellular functions such as survival, proliferation, migration and in various types of cells **(Dancey, 2004; Teiten *et al.*, 2010)**. The stimulation of this pathway begins with the activation of receptor tyrosine kinases, which promotes the recruitment and activation of PI3K family members. PI3K phosphorylates phosphoinositides (PIPs) at the 3-hydroxyl of the inositol ring. These phosphorylated phospholipids (PI3Ps), act as membrane tethers for many PI3K downstream effector proteins with pleckstrin homology (PH) regions **(Storz and Toker, 2002)**. PI3Ks can additionally be activated by signaling mediated by G-protein coupled receptors and Ras **(Katso *et al.*, 2001)**. Upon activation, PI3Ks phosphorylate phosphatidylinositol-4,5-bisphosphate (PIP2) to convert it to phosphatidylinositol-3,4,5-trisphosphate (PIP3), a process opposed by phosphatase and tensin homolog (PTEN) **(Carracedo *et al.*, 2008)**. Effector proteins phospholipid-dependentkinase 1 (PDK1) and Akt are activated through the binding of their PH domains to lipid products of PI3K on the plasma membrane. PDK1 is a serine/threonine protein kinase that phosphorylates several members of the conserved AGC kinase superfamily [comprising the prototype protein kinases A (PKA), B

(PKB) and C (PKC)] **(Storz and Toker, 2002)**. Akt is a key domino in determining whether a cell will survive and proliferate, undergo apoptosis or senescence **(Harikumar *et al.*, 2010)**. Phosphorylation of Akt and mTOR is significantly correlated, and deregulation of PI3K/Akt/mTOR signaling may lead to uncontrolled protein synthesis and cell cycle progression **(Kesari *et al.*, 2005)**.

SUMMARY, CONCLUSIONS, AND FUTURE PERSPECTIVES

Although data from several studies dealing with molecular mechanisms through natural substances effect the cells were obtained, several open questions remain still unknown. The mTOR signaling network is likely to be very complex, including crosstalk and feedback mechanisms**.** Agents that inhibit the downstream protein kinase mTOR as well as agents that inhibit multiple kinases including components of the PI3K-Akt pathway are under clinical evaluation. Nowadays, natural substances, including resveratrol, occur to be able to effect cell processes through PI3K/Akt/m TOR signaling pathway.

Acknowledgments: Our research was supported by VEGA scientific grant no. 1/0790/11 and no. 1/0084/12.

REFERENCES

AGGARVALL, B. B. - VAN KUIKEN, M. E. - IYER, L. H. - SUNG, B. 2009. Molecular Targets of Nutraceuticals Derived from Dietary Spices: Potential Role in Suppression of Inflammation and Tumorigenesis. In *Experimental Biology and Medicine*, vol. 234, 2009, no. 8, p. 825-849.

AGGARWAL, B. B. 2010. Resveratrol, a multitargeted agent, can enhance antitumor activity of gemcitabine in vitro and in orthotopic mouse model of human pancreatic cancer. In *International Journal of Cancer*, vol. 127, 2010, no. 2, p. 257–268.

ATHAR, M. - BACK, J. H. - KOPELOVICH, L. - BICKERS, D. R. - KIM, A. L. 2009. Multiple molecular targets of resveratrol: Anti-carcinogenic mechanisms. In *Archives of Biochemistry and Biophysics*, vol. 486, 2009, no. 2, p. 95-102.

BAI, Y. - MAO, Q. Q. - QIN, J. - ZHENG, X. Y. - WANG, Y. B. - YANG, K. - SHEN, H. F. - XIE, L. P. 2010. Resveratrol induces apoptosis and cell cycle arrest of human T24 bladder

cancer cells in vitro and inhibits tumor growth in vivo. In *Cancer Science*, vol. 101, 2010, no. 2, p. 488-493.

BJORNSTI, M. A. - HOUGHTON, P. J. 2004. The TOR pathway: a target for cancer terapy. In *Nature reviews Canver*, vol. 4, 2004, no. 5, p. 335-348.

BRITO, P. M. - DEVILLARD, R. - NÉGRE-SALVAYRE, A. - ALMEIDA, L. M. - DINIS, T. C. - SALVAYRE, R. - AUGÉ, N. 2009. Resveratrol inhibits the mTOR mitogenic signaling evoked by oxidized LDL in smooth muscle cells. In *Atherosclerosis*, vol. 205, 2009, no. 1, p. 126-134.

BROWER, V. 1998. Nutraceuticals: Poised for a healthy slice of the healthcare market? In *Nature Biotechnology*, vol. 16, 1998, no. 8, p. 728–731.

CADENAS, S. - BARJA, G. 1999. Resveratrol, melatonin, vitamin E, and PBN protect against renal oxidative DNA damage induced by the kidney carcinogen KBrO3. In *Free Radical Biology & Medicine*, vol. 26, 1999, no. 11/12 , p. 1531-1537.

CARRACEDO, A. - MA, L. - TERUYA-FELDSTEIN, J. - ROJO, F. - SALMENA, L. - ALIMONTI, A. - EGIA, A. - SASAKI, A. T. - THOMAS, G. - KOZMA, S. C. - PAPA, A. - NARDELLA, C. - CANTLEY, L. C. - BASELGA, J. - PANDOLFI, P. P. 2008. Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. In *Journal of Clinical Investigation*, vol. 118, 2008, no. 9, p. 3065–3074.

DANCEY, J. E. 2004. Molecular targeting: PI3 kinase pathway. In *Annals of Oncology*, vol. 15, 2004, no. 4, p. 233–239.

DAS, D. K. - MAULIK, N. 2006. Resveratrol in cardioprotection: A therapeutic promise of alternative medicine. In *Molecular Interventions,* vol. 6, 2006, p. 36–47.

DOWNING, J. A. - SCARAMUZZI, R. J. 1991. Nutrient effects on ovulation rate, ovarian function and the secretion of gonadotrophic and metabolic hormones in sheep. In *Journal of Reproduction and Fertility Supplement*, vol. 43, 1991, p. 209–227.

DUTCHER, J. P. 2004. Mammalian target of rapamycin inhibition. In *Clinical Cancer Research*, vol. 10, 2004, p. 6382-7.

FINGAR, D. C. - RICHARDSON, C. J. - TEE, A. R. - CHEATHAM, I. - TSOU, C. - BLENIS, J. 2004. mTOR controls cell cycle progression through its cell growth effectors S6K1 and 4E-BP1/eukaryotic translation initiation factor 4E. In *Mollecular and Cellular Biology*, vol. 24, 2004, no. 1, p. 200-216.

HARIKUMAR, K. B. - KUNNUMAKKARA, A. B. - SETHI, G. - DIAGARADJANE, P. - ANAND, P. - PANDEY, M. K. - GELOVANI, J. - KRISHNAN, S. - GUHA, S. -

HATTORI, R. - OTANI, H. - MAULIK, N. - DAS, D. K. 2002. Pharmacological preconditioning with resveratrol: role of nitric oxide. *American Journal of Physiology - Heart and Circulatory Physiol*ogy, vol. 282, 2002, p. 1988-1995.

HEAPE, W. 1899. Abortion, barrenness, and fertility in sheep: an abstract of records obtained for the year 1896–1897. In *Journal of the Royal Agricultural Society* (third series), vol. 10, 1899, no. 27, p. 217*–248.*

JIANG, H. - ZHANG, L. - KUO, J. - KUO, K. - GAUTAM, S. C. - GROC, L. - RODRIGUEZ, A. I. - KOUBI, D. - HUNTER, T. J. - CORCORAN, G. B. - SEIDMAN, M. D. - LEVINE, R. A. 2005. Resveratrol-induced apoptotic death in human U251 glioma cells. In *Molecular Cancer Therapy*, vol. 4, 2005, no. 4, p. 554–561.

JIANG, H. - ZHANG, L. - KUO, J. - KUO, K. - GAUTAM, S. C. - GROC, L. - SHANKAR, S. - CHEN, Q. - SIDDIQUI, I. - SARVA, K. - SRIVASTAVA, R. K. 2007. Sensitization of TRAIL-resistant LNCaP cells by resveratrol (3, 49, 5 tri-hydroxystilbene): molecular mechanisms and therapeutic potential. In *Journal of Molecular Signaling*, vol. 2, 2007, no. 7.

JOE, A. K. - LIU, H. - SUZUI, M. - VURAL, M. E. - XIAO, D. - WEINSTEIN, I. B. 2002. Resveratrol induces growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines. In *Clinical Cancer Research*, vol. 8, 2002, p. 893–903.

KATSO, R. - OKKENHAUG, K. - AHMADI, K. - WHITE, S. - TIMMS, J. et al. 2001. Cellular function of phosphoinositide 3-kinases: implications for development, homeostasis, and cancer. In *Annual Review of Cell and Developmental Biology*, vol. 17, 2001, p. 615–675.

KESARI, S. - RAMAKRISHNA, N. - SAUVAGEOT, C. - STILES, C. D. - WEN, P. Y. 2005. Targeted molecular therapy of malignant gliomas. In *Current Neurology Neuroscience Reports*, vol. 5, 2005, no. 3, p. 186-97.

KOLESÁROVÁ, A. - CAPCAROVÁ, M. - BAKOVÁ, Z. - GÁLIK, B. - JURÁČEK, M. - ŠIMKO, M. - SIROTKIN, A.V. 2011. The effect of bee pollen on secretion activity, markers of proliferation and apoptosis of porcine ovarian granulosa cells *in vitro*. In *Journal of Environmental Science and Health, Part B*, vol. 46, 2011, no. 3, p. 207-212.

LEE, M. H. - CHOI, B. Y. - KUNDU, J. K. - SHIN, Y. K. - NA, H. K. 2009. Resveratrol suppresses growth of human ovarian cancer cells in culture and in a murine xenograft model: eukaryotic elongation factor 1A2 as a potential target. In *Cancer Research*, vol. 69, 2009, no. 18, p. 7449–7458.

LI, H. - WU, W. K. - ZHENG, Z. - CHE, C. T. - YU, L. 2009. 2,39,4,49,59- Pentamethoxy-trans-stilbene, a resveratrol derivative, is a potent inducer of apoptosis in colon cancer cells via targeting microtubules. In *Biochemical Pharmacology*, vol. 78, 2009, p. 1224–1232.

LIU, P. L. - TSAI, J. R. - CHARLES, A. L. - HWANG, J. J. - CHOU, S. H. - PING, Y. H. - LIN, F. Y. - CHEN, Y. L. - HUNG, CH. Y. - CHEN, W. Y. - CHEN, Y. H. - CHONG, I. W. 2010. Resveratrol inhibits human lung adenocarcinoma cell metastasis by suppressing heme oxygenase 1-mediated nuclear factor-kappaB pathway and subsequently downregulating expression of matrix metalloproteinases. In *Molecular Nutrition and Food Research*, vol. 54, 2010, no. 2, p. 196–204.

LÓPEZ-VÉLEZ, M. - MARTÍNEZ, F. - VALLE-RIBES, C. D. 2003. The Study of Phenolic Compounds as Natural Antioxidants in Wine. In *Critical Reviews in Food Science and Nutrition*, vol. 43, 2003, no. 3, p. 233-244.

MANNING, B. D. 2004. Balancing Akt with S6K: implications for both metabolic diseases and tumorigenesis. In *Journal of Cell Biology*, vol. 167**,** 2004, no. 3, p. 399–403.

MARSHALL, F. H. A. 1904. Fertility in sheep. In *Transactions of the Highland Agricultural Society*, vol.16, 1904, p. 34-43.

MELZOCH, K. - FILIP, V. - BUCKIOVÁ, D. - HANZLÍKOVÁ, I. - ŠMIDRKAL, J. 2000. Resveratrol – occurrence in wine originating from Czech vineyard regions and effect on human health. In *Czech Journal of Food Sciences*, vol. 18, 2000, p. 35-40.

MONGET, P. - MARTIN, G. B. 1997. Involvement of insuline-like growth factors in the interaction between nutrition and reproduction in female mammals. In *Human Reproduction Volume*, vol. 12, 1997, no. 1, p. 33-52.

MUKHERJEE, S. - DUDLEY, J. I. - DAS, D. K. 2010. Dose-dependency of resveratrol in providing health benefits. In *Dose Response*, vol. 8, 2010, no. 4, p. 478-500.

POLANS, A. S. 2007. Resveratrol inhibits tumor growth of human neuroblastoma and mediates apoptosis by directly targeting mitochondria. In *Clinical Cancer Research*, vol. 17, 2007, no. 13, p. 5162-5169.

PRUNIER, A. - QUESNEL, H. 2000. Influence of the nutritional status on ovarian development in female pigs. In *Animal Reproduction Science*, vol. 60/61, 2000, p. 185-197.

ROCHA-GONZÁLES, H. I. - AMBRIZ-TUTUTI, M. - GRANADOS-SOTO, V. 2008. Resveratrol: A Natural Compound with Pharmacological Potential in Neurodegenerative Diseases. In *CNS Neuroscience & Therapeutics*, vol. 14, 2008, no. 3, p. 234-247.

SHANKAR, S. - SINGH, G. - SRIVASTAVA, R. K. 2007a. Chemoprevention by resveratrol: Molecular mechanisms and therapeutic potential. In *Frontiers in Bioscience*, vol. 12, 2007, p. 4839-4854.

SHANKAR, S. - SIDDIQUI, I. - SRIVASTAVA, R. K. 2007b. Molecular mechanisms of resveratrol (3,4,5-trihydroxy-trans-stilbene) and its interaction with TNF-related apoptosis inducing ligand (TRAIL) in androgen-insensitive prostate cancer cells. In *Mollecular and Cellular Biochemistry*, vol. 304, 2007, no. 1/2, p. 273–285.

SCHMELZLE, T. - HALL, M. N. 2000. TOR, a central controller of cell growth. In *Cell*, vol. 103, 2000, no. 2, p. 253-262.

SLUSARZ, A. - SHENOUDA, N. S. - SAKLA, M. S. - DRENKHAHN, S. K. - NARULA, A. S. - MAC DONALD, R. S. - BESCH-WILLIFORD, C. L. - LUBAHN, D. B. 2010. Common botanical compounds inhibit the hedgehog signaling pathway in prostate cancer. In *Cancer Research*, vol. 70, 2010, no. 8, p. 3382-3390.

SOLEAS, G. J. - GRASS, L. - JOSEPHY, P. D. - GOLDBERG, D. M. - DIAMANDIS, E. P. 2006. A comparison of the anticarcinogenic properties of four red wine polyphenols. In *Clinical Biochemistry*, vol. 35, 2006, no. 2, p. 492-7.

SRIVASTAVA, R. K. - UNTERMAN, T. G. - SHANKAR, S. 2010. FOXO transcription factors and VEGF neutralizing antibody enhance antiangiogenic effects of resveratrol. In *Molecular and Cellular Biochemistry*, vol. 337, 2010, no. 1/2, p. 201-212.

STORZ, P. - TOKER, A. 2002. 30-phosphoinositide-dependent kinase-1 (PDK-1) in PI 3-kinase signaling. In *Frontiers of Bioscience*, vol. 7, 2002, p. 886-902.

SUBASH, C. - GUPTA, J. - HYE, K. - SAHDEO, P. - BHARAT, B. 2010. Regulation of survival, proliferation; invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals. In *Cancer Metastasis Reviews*, vol. 29, 2010, no. 3, p. 405-434.

SUN, C. - HU, Y. - LIU, X. - WU, T. - WANG, Y. - HE, W. - WEI, W. 2006. Resveratrol downregulates the constitutional activation of nuclear factor-kappaB in multiple myeloma cells, leading to suppression of proliferation and invasion, arrest of cell cycle, and induction of apoptosis. In *Cancer Genet Cytogenet*, vol. 165, 2006, no. , p. 9-19.

TEITEN, M. H. - EIFES, S. - DICATO, M. - DIEDERICH, M. 2010. Curcumin—The Paradigm of a Multi-Target Natural Compound with Applications in Cancer Prevention and Treatment. In *Toxins*, vol. 2, 2010, p. 128-162.

VAN GINKEL, P. R. - SAREEN, D. - SUBRAMANIAN, L. - WALKER, Q. - DARJATMOKO, S.R. - LINDSTROM, M. J. - KULKARNI, A. - ALBERT, D. M. - WU, J.

Y - TSAI, K. W. - SHEE, J. J. - LI, Y. Z. - CHEN, C. H. 2010. 49-Chloro-3,5-dihydroxystilbene, a resveratrol derivative, induces lung cancer cell death. In *Acta Pharmacol Sin*, vol. 31, 2010, p. 81-92.

WANG, S., YANG, D. - LIPPMAN, M. E. 2003. Targeting Bcl-2 and Bcl-XL with nonpeptidic small-molecule antagonists. In *Seminars in Oncology*, vol. 30, 2003, no. 16, p. 133-142.

WU, J. Y. - TSAI, K. W. - SHEE, J. J. - LI, Y. Z. - CHEN, CH. - CHUANG, J. J. - LIU, Y. W. 2010. 49-Chloro-3,5-dihydroxystilbene, a resveratrol derivative, induces lung cancer cell death. In *Acta Pharmacologica Sinica*, vol. 31, 2010, no. 1, p. 81-92.

ZEISEL, S. H. 1999. Regulation of "nutraceuticals". In *Science*, vol. 285, 1999, no. 5435, p. 1853-1855.