

## Bölüm 6

### KAPSAİSİN VE KANSER

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#### GİRİŞ

Bazı günlük tüketilen meyve ve sebzelerde yaygın olarak bulunan doğal fitokimyasalların, moleküler ve hücresele seviyelerde çeşitli kanser türleri üzerinde engelleyici etkileri olduğu iyi bilinmektedir (Aggarwal, Takada & Oommen, 2004). Doğal olarak oluşan bu fitokimyasallardan biri olan kapsaisin, gıda katkı maddesi olarak yaygın bir şekilde kullanılan Capsicum (Family Solanaceae) cinsi acı biberlerin keskin bir ana bileşenidir. Kapsaisinin, çeşitli fizyolojik ve farmakolojik etkileri olduğu gösterilmiştir (Szallasi & Blumberg, 1999). Örneğin çeşitli çalışmalar, kapsaisin kullanımının, bazı hastalıklar ve kanserle ilişkili iltihap ve ağrıyı hafifletebileceğini göstermektedir (Hayman & Kam, 2008). Ayrıca biriktirme çalışmaları, kapsaisinin lösemi (Ito & ark., 2004, Tsou & ark., 2006), multipl miyelom (Bhutani & ark., 2007), kutanöz hücre karsinoması (Hail & Lotan 2002), glioma (Lee, Nam & Kim, 2000, Amantini & ark., 2007), dil kanseri (Ip & ark., 2012a), nazofarengeal karsinom (Ip & ark., 2012b), özofagus karsinoması (Wu & ark., 2006), gastrik kanser (Kim & ark., 1997), pankreas kanseri (Zhang & ark., 2008, Pramanik, Boreddy & Srivastava, 2011), hepatokarsinom (Jung, Kang & Moon, 2001, Huang & ark., 2009), kolon kanseri (Kim & ark., 2004, Lu & ark., 2010), küçük hücreli akciğer kanseri (Brown & ark., 2010), meme kanseri (Thoenissen & ark., 2010) ve prostat kanserinde (Mori & ark., 2006, Sánchez & ark., 2007) dahil olmak üzere insanlarda çeşitli kanser hücre hatları üzerinde anti-proliferatif etkiye sahip olduğunu göstermiştir. Kapsaisin, kanser hücrelerinin büyümesini baskılayabilme kapasitesine, öncelikli olarak apoptozun indüklenmesi yoluyla aracılık ettiği düşünülmektedir. Ek olarak, kapsaisinin anti-kanser etkileri arasında hücre döngüsünün ilerlemesinin durdurulması, transkripsiyon faktörünün düzenlenmesinin yer aldığı düşünülmektedir (Lin & ark., 2013).

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ve apoptozuindüklemesine yol açıp açmadığını ve mitokondri ve kaspaz üyelerinin programlanmış hücre ölümüne katılıp katılmadıklarını belirledik. Burada, kapsaisin'in G2 / M fazında hücre döngüsünün durmasına neden olduğunu ve KB hücrelerinin apoptozuna neden olduğunu gösteriyoruz. KB hücrelerinde kapsaisin kaynaklı apoptoz, mitokondriyal membran geçirgenliği ve kaspaz aktivasyonu ile ilişkilidir. Bu sonuçlar, kapsaisinin, kanser hücresi büyümesinin önlenmesinde faydalı olabileceğini ortaya koymaktadır (Lin & ark., 2013). Üstelik yüksek oranda potansiyel olarak çoklu etki mekanizmasına sahip olan bir pleitrofik molekül olarak, kapsaisinin birçok yol aracılığıyla çalışması ve bunların birçoğunun TRPV1 reseptörünün aktivasyonunu içermemesi muhtemeldir. Kanserojenlerin metabolik aktivasyonunun inhibe edilmesi ve çok çeşitli kanser hücrelerinde apoptozun indüklenmesi dışında, kapsaisinin antikanser aktiviteleri arasında hesaba katılması önerilen mekanizmalar antioksidan aktivite (Dairam & ark., 2008), peroksizom proliferatör ile aktive edilmiş reseptör gama aktivasyonu (Kim ve ark 2004), anjiyogenezin inhibisyonu (Min & ark., 2004), kansere bağlı lipit metabolizmasının modülasyonu (Anandakumar & ark., 2009) ve aromataz aktivite inhibisyonu (Luqman& ark., 2011) bulunmaktadır (Bley & ark., 2012).

## KAYNAKÇA

- Adaszek, L. Gadomska, D. Mazurek, L. Pawel, LYP. Madany, J. Winiarczyk, S. (2018). Properties of capsaicin and its utility in veterinary and human medicine. *Research in Veterinary Science*, 123:14-19. Doi: <https://doi.org/10.1016/j.rvsc.2018.12.002>
- Aggarwal, BB. Takada, Y. Oommen, OV. (2004). From chemoprevention to chemotherapy: common targets and common goals. *Expert Opinion Investigational Drugs*, 13(10):1327-38. Doi: 10.1517/13543784.13.10.1327
- Amantini, C. Mosca, M. Nabissi, M. Lucciarini, R. Caprodossi, S. Arcella, A. Giangaspero, F. Santoni, G. (2007). Capsaicin-induced apoptosis of glioma cells is mediated by TRPV1 vanilloid receptor and requires p38 MAPK activation. *Journal Neurochem*, 102:977-990.
- Anandakumar, P. Jagan, S. Kamaraj, S. Ramakrishnan, G. Clara, J. B. Pathitha, D. Kavitha, T. & Devaki, T. (2009). Ameliorating effect of capsaicin on alterations in lipid metabolism during mice lung carcinoma. *Arch Pharm Research*, 32, 229-34.
- Anandakumar, P. Kamaraj, S. Jagan, S. Ramakrishnan, G. Asokkumar, S. Naveenkumar, C. Raghunandhakumar, S. Devaki, T. (2012). Capsaicin inhibits benzo(a)pyrene-induced lung carcinogenesis in an in vivo mouse model. *Inflammation Researchs*, 61, 1169-1175.
- Athanasiou, A. Smith, P.A. Vakilpour, S. Kumaran, N.M. Turner, A.E. Bagiokou, D. Layfield, R. Ray, D. E. Westwell, A. D. Alexander, S. P. Kendall, D. A. Lobo, D. N. Watson, S. A. Lophatanon, A. Muir, K.A. Guo, D.A. & Bates, T. E. (2007). Vanilloid receptor agonists and antagonists are mitochondrial inhibitors: How vanilloids cause non-vanilloid receptor mediated cell death. *Biochem Biophys Res Commun*, 354, 50-5. Doi: 10.1016/j.bbrc.2006.12.179
- Bhutani, M. Pathak, AK. Nair, AS. Kunnunakkara, AB. Guh, S. Sethi, G. Aggarwal,

- BB. (2007). Capsaicin is a novel blocker of constitutive and interleukin-6 -inducible STAT3 activation. *Clinical Cancer Research*, 13:3024–3032.
- Bley, K., Boorman, G., Mohammad, B., Mckenzie, D., And Babbar, S. (2012) A Comprehensive Review of the Carcinogenic and Anticarcinogenic Potential of Capsaicin. *Toxicologic Pathology*, 40: 847-873.
- Bode, A.M. & Dong, Z. (2011). The two faces of capsaicin. *Cancer Research*, 71,2809–2814. Doi: 10.1158/0008-5472.CAN-10-3756
- Brown, KC. Witte, TR. Hardman, WE. Luo, H. Chen, YC. Carpenter, AB. Lau, JK. Dasgupt, P. (2010). Capsaicin displays anti-proliferative activity against human small cell lung cancer in cell culture and nude mice models via the E2F pathway. *PLoS One*, 5:e10243. Doi: 10.1371/journal.pone.0010243
- Chang, H.C. Chen, S.T. Chien, S.Y. Kuo, S.J. Tsai, H.T. Chen, D.R. (2011). Capsaicin may induce breast cancer cell death through apoptosis-inducing factor involving mitochondrial dysfunction. *Human & Experimental Toxicology*, 30, 1657–1665. Doi: <https://doi.org/10.1177/09603271110396530>
- Czaja MJ. (2002). Induction and regulation of hepatocyte apoptosis by oxidative stress. *Antioxidants & Redox Signaling*, 4: 759-67. Doi: <https://doi.org/10.1089/152308602760598909>
- Dairam, A. Fogel, R. Daya, S. & Limson, J. L. (2008). Antioxidant and iron-binding properties of curcumin, capsaicin, and S-allylcysteine reduce oxidative stress in rat brain homogenate. *Journal Agricultural and Food Chemistry*, 56, 3350–6. Doi: 10.1021/jf0734931
- de-Sa-Junior, P.L. Pasqualoto, K.F. Ferreira, A.K. Tavares, M.T. Damiao, M.C. de Azevedo, R.A. Camara, D.A. Pereira, A. de Souza, D.M. Parise Filho, R. (2013). RPF101, a new capsaicin-like analogue, disrupts the microtubule network accompanied by arrest in the G2/M phase, inducing apoptosis and mitotic catastrophe in the MCF-7 breast cancer cells. *Toxicology and Applied Pharmacology*, 266(3):385-98. Doi: 10.1016/j.taap.2012.11.029
- El-kotta, A.F. & Bin-Meferij, M.M. (2018). Suppressive effects of capsaicin against N-nitrosomethylurea-induced mammary tumorigenesis in rats. *Biomedicine & Pharmacotherapy*, 98:673-679. Doi: <https://doi.org/10.1016/j.biopha.2017.12.036>
- Elmore, S. (2007). Apoptosis: a review of programmed cell death. *NIH Public Access, Toxicol Pathol*, 35:495–516.
- Erdost, H. (2004). Capsaicin. *Uludağ Üniversitesi J. Fac. Vet. Med*, 23,1-2-3:149-155.
- Fulda, S. & Debatin, KM. (2006). Extrinsic versus intrinsic apoptosis pathways in anti-cancer chemotherapy. *Oncogene*, 25:4798–4811. Doi: 10.1038/sj.onc.1209608
- Gottesman, M.M. Fojo, T. Bates, S.E. (2002). Multidrug resistance in cancer: Role of ATP-dependent transporters. *Nature Reviews Cancer*;2:48–58. Doi: 10.1038/nrc706.
- Hail, N Jr. & Lotan, R. (2002). Examining the role of mitochondrial respiration in vanilloid-induced apoptosis. *Journal National Cancer Institute*, 94:1281–1292. Doi: <https://doi.org/10.1093/jnci/94.17.1281>
- Hanahan, D. & Weinberg R. A. (2000). The hallmarks of cancer. *Cell*, 100:57–70. Doi: 10.1016/S0092-8674(00)81683-9
- Hayman, M. & Kam, PC. (2008). Capsaicin: a review of its pharmacology and clinical applications. *Curr Anest Crit Care*, 19(5):338–343. Doi: 10.1016/j.cacc.2008.07.003.
- Hengartner, MO. (2000). The biochemistry of apoptosis. *Nature*, 407(6805):770-6. Doi: 10.1038/35037710.
- Hoch-Ligeti, C. (1951). Production of liver tumours by dietary means; effect of feeding chilies [*Capsicum frutescens* and *annuum* (Linn.)] to rats. *Acta – Unio Int. Contra*

- Cancer*, 7, 606–611.
- Huang, SP. Chen, JC. Wu, CC. Chen, CT. Tang, NY. Ho, YT. Lo, C. Lin, JP. Chung, JG. Lin, JG. (2009). Capsaicin-induced apoptosis in human hepatoma HepG2 cells. *Anti-cancer Research*, 29(1):165-74.
- Huh, H.C. Lee, S.Y. Lee, S.K. Park, N.H. Han, I.S. (2011). Capsaicin induces apoptosis of cisplatin-resistant stomach cancer cells by causing degradation of cisplatin-inducible Aurora-A protein. *Nutr Cancer*, 63(7):1095-103. Doi: 10.1080/01635581.
- Ip, SW. Lan, SH. Huang, AC. Yang, JS. Chen, YY. Huang, HY. Lin, ZP. Hsu, YM. Yang, MD. Chiu, CF. Chung, JG. (2012/a). Capsaicin induces apoptosis in SCC-4 human tongue cancer cells through mitochondria-dependent and independent pathways. *Environmental Toxicology*, 27(6):332-41. Doi: 10.1002/tox.20646
- Ip, SW. Lan, SH. Lu, HF. Huang, AC. Yang, JS. Lin, JP. Huang, HY. Lien, JC. Ho, CC. Chiu, CF. Wood, W. Chung, JG. (2012/b). Capsaicin mediates apoptosis in human nasopharyngeal carcinoma NPC-TW 039 cells through mitochondrial depolarization and endoplasmic reticulum stress. *Human & Experimental Toxicology*, 31(6):539-49. Doi: 10.1177/0960327111417269
- Ito, K. Nakazato, T. Yamato, K. Miyakawa, Y. Yamada, T. Hozumi, N. Segawa, K. Ikeda, Y. Kizaki, M. (2004). Induction of apoptosis in leukemic cells by homovanillic acid derivative, capsaicin, through oxidative stress: implication of phosphorylation of p53 at Ser-15 residue by reactive oxygen species. *Cancer Research*, 64(3):1071-8.
- Jung, MY. Kang, HJ. Moon, A. (2001). Capsaicin-induced apoptosis in SK-Hep-1 hepatocarcinoma cells involves Bcl-2 downregulation and caspase-3 activation. *Cancer Letters*, 165(2):139-45. Doi: [https://doi.org/10.1016/S0304-3835\(01\)00426-8](https://doi.org/10.1016/S0304-3835(01)00426-8)
- Jung, SH. Kim, HJ. Oh, GS. Shen, AH. Lee, S. et al. (2014). Capsaicin ameliorates cisplatin-induced renal injury through induction of Heme Oxygenase-1. *Molecules and Cells*, 37(3):234-40. Doi: 10.14348/molcells.2014.2322
- Kim, C. S. Park, W. H. Park, J. Y. Kang, J. H. Kim, M. O. Kawada, T. Yoo, H. Han, I. S. & Yu, R. (2004). Capsaicin, a spicy component of hot pepper, induces apoptosis by activation of the peroxisome proliferator-activated receptor gamma in HT-29 human colon cancer cells. *Journal of Medicinal Food*, 7(3):267-73. Doi: 10.1089/jmf.2004.7.267
- Kim, JD. Kim, JM. Pyo, JO. Kim, SY. Kim, BS. Yu, R. Han, IS. (1997). Capsaicin can alter the expression of tumor forming-related genes which might be followed by induction of apoptosis of a Korean stomach cancer cell line, SNU-1. *Cancer Letters*, 120(2):235-41.
- Lee, S. Kumar S. (1980). Metabolism in vitro of capsaicin, a pungent principle of red pepper, with rat liver microsomes. *Academic Press*, New York.
- Lee, YS. Nam, DH. Kim, JA. (2000). Induction of apoptosis by capsaicin in A172 human glioblastoma cells. *Cancer Letters*, 161(1):121–130.
- Lehen'kyi, V. & Prevarskaya, N. (2011). Oncogenic TRP channels. *Advances in Experimental Medicine and Biology*, 704:929-45. Doi: 10.1007/978-94-007-0265-3\_48
- Li, H. Krstin, S. Wang, S. Wink, M. (2018). Capsaicin and piperine can overcome multidrug resistance in cancer cells to doxorubicin. *Molecules*, 23(3), 557. Doi:10.3390/molecules23030557
- Lin, C.H. Lu, W.C. Wang, C.W. Chan, Y.C. Chen, M.K. (2013). Capsaicin induces cell cycle arrest and apoptosis in human KB cancer cells. *BMC Complementary and Alternative Medicine*, 25;13:46. Doi: 10.1186/1472-6882-13-46.
- Lin, R.J. Wu, I.J. Hong, J.Y. Liu, B.H. Liang, R.Y. Yuan, T.M. Chuang, S.M. (2018). Capsaicin-induced TRIB3 upregulation promotes apoptosis in cancer cells. *Cancer*

- Management and Research*, 4;10:4237-4248. Doi: 10.2147/CMAR.S162383
- Liu, N.C. Hsieh, P.F. Hsieh, M.K. Zeng, Z.M. Cheng, H.L. Liao, J.W.,Chueh, P.J. (2012). Capsaicin-mediated tNOX (ENOX2) up-regulation enhances cell proliferation and migration in vitro and in vivo. *Journal of Agricultural and Food Chemistry*, 60(10):2758-65. Doi: 10.1021/jf204869w
- Lopez-Carrillo, L. Camargo, M.C. Schneider, B.G. Sicinschi, L.A. HernandezRamirez, R.U, Correa, P. Cebrian, M.E. (2012). Capsaicin consumption, Helicobacter pylori CagA status and IL1B-31C4T genotypes: a host and environment interaction in gastric cancer. *Food Chemical Toxicology*, 50(6), 2118–2122. Doi:10.1016/j.fct.2012.02.043
- Lu, H.F. Chen, Y.L, Yang, J.S. Yang, Y.Y. Liu, J.Y. Hsu, S.C. Lai, K.C. Chung, J.G. (2010). Antitumor activity of capsaicin on human colon cancer cells in vitro and colo 205 tumor xenografts in vivo. *Journal of Agricultural and Food Chemistry*, 58(24):12999-3005. Doi: 10.1021/jf103335w
- Luqman, S. Meena, A. Marler, L. E. Kondratyuk, T. P. & Pezzuto, J. M. (2011). Suppression of tumor necrosis factor-a-induced nuclear factor B activation and aromatase activity by capsaicin and its analog capsazepine. *Journal of Medicinal Food*, 14(11):1344-51. Doi: 10.1089/jmf.2010.0236
- Min, J. K. Han, K. Y. Kim, E. C. Kim, Y. M. Lee, S. W. Kim, O. H. Kim, K. W. Gho, Y. S. & Kwon, Y. G. (2004). Capsaicin inhibits in vitro and in vivo angiogenesis. *Cancer Research*, 64(2):644-51.
- Moon, D.O. Kang, C.H. Kang, S.H. Choi, Y.H. Hyun, J.W. Chang, W.Y. Kang, H.K. Koh, Y.S. Maeng, Y.H. Kim, Y.R. Kim, G.Y. (2012). Capsaicin sensitizes TRAIL-induced apoptosis through Sp1-mediated DR5 up-regulation: involvement of Ca(2b) influx. *Toxicology and Applied Pharmacology*, 259(1):87-95. Doi: 10.1016/j.taap.2011.12.010
- Mori, A. Lehmann, S. O'Kelly, J. Kumagai, T. Desmond, J.C. Pervan, M. McBride, W.H. Kizaki, M. Koeffler, H.P. (2006). Capsaicin, a component of red peppers, inhibits the growth of androgen-independent, p53 mutant prostate cancer cells. *Cancer Research*, 66(6):3222-9. Doi: 10.1158/0008-5472.CAN-05-0087
- Parashar, P. Tripathi, C.B. Arya, M. Kanoujia, J. Singh, M. Yadav, A. Kaithwas, G. Saraf, S.A. (2019). A synergistic approach for management of lung carcinoma through folic acid functionalized co-therapy of capsaicin and gefitinib nanoparticles: Enhanced apoptosis and metalloproteinase-9 down-regulation. *Phytomedicine*, 53:107-123. Doi: <https://doi.org/10.1016/j.phymed.2018.09.013>.
- Peker, S. (2015). Capsaicin'in ovaryum granuloza hücrelerinin proliferasyonu ve apoptozisi üzerine etkisi. Uludağ Üniversitesi, Sağlık Bilimleri Enstitüsü, Doktora Tezi.
- Pramanik, K.C. Boreddy, S.R. Srivastava, S.K. (2011). Role of mitochondrial electron transport chain complexes in capsaicin mediated oxidative stress leading to apoptosis in pancreatic cancer cells. *PLoS One*, 6(5):e20151. Doi: 10.1371/journal.pone.0020151
- Raisinghani, M. Pabbidi, R.M. Premkumar, L.S. (2005). Activation of transient receptor potential vanilloid 1 (TRPV1) by resiniferatoxin. *The Journal of Physiology*, 567(Pt 3):771-86. Doi: 10.1113/jphysiol.2005.087874.
- Reilly, C. A. Ehlhardt, W. J. Jackson, D. A. Kulanthaivel, P. Mutlib, A. E. Espina, R. J. Moody, D. E. Crouch, D. J. & Yost, G. S. (2003). Metabolism of capsaicin by cytochrome P450 produces novel dehydrogenated metabolites and decreases cytotoxicity to lung and liver cells. *Chemical Research in Toxicology*, 16(3), 336–49. Doi: 10.1021/tx025599.
- Sánchez, AM. Malagarie-Cazenave, S. Olea, N. Vara, D. Chiloeches, A. DíazLaviada, I. (2007). Apoptosis induced by capsaicin in prostate PC-3 cells involves ceramide ac-



- cumulation, neutral sphingomyelinase, and JNK activation. *Apoptosis*, 12(11):2013-24. Doi: 10.1007/s10495-007-0119-z
- Sharma, S. K. Vijb, A. S. Sharma, M. (2013) Mechanisms and clinical uses of capsaicin. *European Journal of Pharmacology*, 720(1-3):55-62. Doi: 10.1016/j.ejphar.2013.10.053
- Singh, S. Sharma, B. Kanwar, S.S. Kumar, A. (2016). Lead Phytochemicals for anticancer drug development. *Frontiers in Plants Science*, 7:1667. Doi: 10.3389/fpls.2016.01667.
- Sugimoto, N. Matsuzaki, K. Katakura, M. Nakamura, H. Ueda, Y. Yachie, A. Shido. O. (2019). Heat attenuates sensitivity of mammalian cells to capsaicin. *Journal of Biochemical Molecular Toxicology*, 23:e22288. Doi: 10.1002/jbt.22288.
- Sun, F. Xiong, S. Zhu, Z. (2016). Dietary capsaicin protects cardiometabolic organs from dysfunction. *Nutrients*, 8(5), 174. Doi: 10.3390/nu8050174.
- Surh, YJ. & Lee, SS. (1996). Capsaicin in hot chili pepper: carcinogen, co-carcinogen or anticarcinogen? *Food and Chemical Toxicology*, 34(3):313-6.
- Szakacs, G. Paterson, JK. Ludwig, JA. Booth-Genthe, C. Gottesman, MM. (2006). Targeting multidrug resistance in cancer. *Nature Reviews Drug Discovery*, 5 : 219-234. Doi: 10.1038 / nrd1984.
- Szallasi, A. & Blumberg, PM. (1999). Vanilloid (capsaicin) receptors and mechanisms. *Pharmacological Reviews*, 51(2):159-212.
- Şener, E. & Sahin, S. (2010). Kapsaisin: farmakokinetik, toksikolojik ve farmakolojik özellikleri. *Hacettepe Üniversitesi Eczacılık Fakültesi Dergisi*; 29: 149-63.
- Thoennissen, NH. O’Kelly, J. Lu, D. Iwanski, GB. La, DT. Abbassi, S. Leiter, A. Karlan, B. Mehta, R. Koeffler, HP. (2010). Capsaicin causes cell-cycle arrest and apoptosis in ER-positive and -negative breast cancer cells by modulating the EGFR/HER-2 pathway. *Oncogene*, 2010, 29:285–296.
- Thyagarajan, B.K.V. & Başkaran, P. (2018). CAP and Metabolic Diseases: A mini review on preclinical mechanisms and clinical efficacy. Gyula Mozsik (Ed.), *Capsaicin and its Human Therapeutic Development* (s.5:75-96). United States: IntechOpen Doi: 10.5772/intechopen.78353
- Tsou, MF. Lu, HF. Chen, SC. Wu, LT. Chen, Y. Ku, HM. Lin, SS. Chung, JG. (2006). Involvement of Bax, Bcl-2, Ca<sup>2+</sup> and caspase-3 in capsaicin-induced apoptosis of human leukemia HL-60 cells. *Anticancer Research*, 26(3A):1965-71.
- Valenzano, K. J. & Sun, Q. (2004). Current perspectives on the therapeutic utility of VR1 antagonists. *Current Medicinal Chemistry*, 11(24):3185-202.
- Vriens, J.& Voets, T. (2018). Sensing the heat with TRPM3. *Pflügers Archiv - European Journal of Physiology*, 470:799–807. Doi: <https://doi.org/10.1007/s00424-017-2100-1>
- Wang, H.M. Chuang, S.M. Su, Y.C. Li, Y.H. Chueh, P.J. (2011). Down-regulation of tumor-associated NADH oxidase, tNOX (ENOX2), enhances capsaicin-induced inhibition of gastric cancer cell growth. *Cell Biochemistry and Biophysics*, 61(2):355-66. Doi: 10.1007/s12013-011-9218-0
- Wu, C. Lin, JP. Yang, JS. Chou, ST. Chen, SC. Lin, YT. Lin, HL. Chung, JG. (2006). Capsaicin induced cell cycle arrest and apoptosis in human esophagus epidermoid carcinoma CE 81 T/VGH cells through the elevation of intracellular reactive oxygen species and Ca<sup>2+</sup> productions and caspase3 activation. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 601(1-2):71-82. Doi: 10.1016/j.mrfmmm.2006.06.015
- Wu, T.T. Peters, A.A. Tan, P.T. Roberts-Thomson, S.J. Monteith, G.R. (2014). Consequences of activating the calcium-permeable ion channel TRPV1 in breast cancer

- cells with regulated TRPV1 expression. *Cell Calcium*, 56(2):59-67. Doi: 10.1016/j.ceca.2014.04.006
- Xu, W. Liu, J. Ma, D. Yuan, G. Lu, Y. Yang, Y. (2017). Capsaicin reduces Alzheimer-associated tau changes in the hippocampus of type 2 diabetes rats. *PLoS One*, 2(2):e0172477. Doi: 10.1371/journal.pone.0172477
- Yang, J. Li, T.Z. Xu, G.H. Luo, B.B. Chen, Y.X. Zhang, T. (2013). Low-concentration capsaicin promotes colorectal cancer metastasis by triggering ROS production and modulating Akt/mTOR and STAT-3 pathways. *Neoplasma*, 60(4):364-72. Doi: 10.4149/neo\_2013\_048
- Yazgan, B. Yazgan, Y. Naziroglu, M. (2016). Ağrı moleküler yollarında TRPV1 katyon kanalının önemi. *Firat Tıp Derg/Firat Med J*, 21(1): 1-10.
- Zhang, J.H. Lai, F.J. Chen, H. Luo, J. Zhang, R.Y. Bu, H.Q. Wang, Z.H., Lin, H.H, Lin, S.Z. (2013). Involvement of the phosphoinositide 3-kinase/Akt pathway in apoptosis induced by capsaicin in the human pancreatic cancer cell line PANC-1. *Oncology Letters*, 5(1):43-48. Doi: 10.3892/ol.2012.991
- Zhang, R. Humphreys, I. Sahu, RP. Shi, Y. Srivastava, SK. (2008). In vitro and in vivo induction of apoptosis by capsaicin in pancreatic cancer cells is mediated through ROS generation and mitochondrial death pathway. *Apoptosis*, 3(12):1465-78. Doi: 10.1007/s10495-008-0278-6
- Ziglioli, F. Frattini, A. Maestroni, U. Dinale, F. Ciuffreda, M. Cortellini, P. (2009). Vanilloid-mediated apoptosis in prostate cancer cells through a TRPV-1 dependent and a TRPV-1-independent mechanism. *Acta Biomed*, 80(1):13-20.