



Coconut: Natural source of potential anticancer agents

● **Amit Ghosh,**

*Assistant professor, Department of Physiology,
All India Institute of Medical Sciences, Bhubaneswar-751019, Odisha, India*

One third to half of all pharmaceutical drugs are originally derived from plants. Natural products are the source of 60% of currently used anticancer products and some of the natural products are under clinical trial. PubMed search shows countless articles on the health benefits of coconut. Curated preventive role of virgin coconut oil (VCO) and coconut water (CW) in cancer, cardiovascular, neuronal, mental and metabolic diseases are reflected in several in vitro and in vivo studies. But underlining causes of these therapeutic effects are yet to be explored. The virgin coconut oil and coconut water have interesting anti-cancer activity. In spite of the miraculous health beneficial effects and potential marketing opportunity, coconut products was not significantly translated into everyday health care products and medicines. This is

because most efforts of drug development efforts are focused on synthetic compounds.

After publication of the FDA's industry guidelines for botanical drug product in June 2004, first botanical product Veregen (sinecatechins) was approved by FDA on 31st October 2006 for marketing. Veregen was prepared from green tea leaves and approved for the topical treatment of perianal and genital condyloma. Approval of veregen by FDA was instrumental in the steadily growing interest for launching of other botanical drug products. Many botanical products are used over thousands of years (due to its beneficial purpose) but according to present FDA rules, identifying the different medicinal properties of its compounds and using them for the formulation of healthcare products will help in getting approval for its marketing for the treatment of specific health condition. New thinking is needed to address this challenge.

In this review we revisit the history of anticancer potential of VCO and summarize the recent findings to expand our understanding about anticancer effect of coconut water. This information will help to understand the mechanism of action and also encourage other research groups to conduct further translational research in this field. Much remains to be discovered with regard to nutritional based treatment. But interpreting the published literature clearly indicates that coconut products function like double edges of a sword – nutritionally it can prevent cancer and it is also a source of potent anticancer molecules. Anticancer properties of coconut oil were also reported by Lim-Sylianco in 1987, in his published 50 years literature review and by Cohen et al. in 1986. Coconut oil is also anti-carcinogenic.

As any promising domain of biology it is better to start with phenotype and then ask “why,” to explore the underlining causes. Anticancer properties of Virgin coconut oil (VCO) are imparted because of its high percentage of medium chain fatty acid. The coconut oil which is composed of 92% saturated fatty acid, are predominantly medium chain fatty acids in the form of triglyceride (MCT) and 8% of unsaturated fatty acids consisting of oleic and linoleic acid as triglycerides.

Table 1: Anticancer role of Ketogenic diet and MCT in animal model.

Anticancer role of ketogenic diet
KD improves the survivability of mouse model of glioma by retarding the tumor growth, prevents reactive oxygen species (ROS) production and shifts tumor tissue gene expression profile towards normal tissue gene expression pattern
KD retards tumor growth in mouse xenograft model
MCT reduces tumor growth and improves nutritional status in GI tract cancer patients
Anticancer effect of MCT, may be exerted through the modulation of immune system
In cachexia-inducing colon adenocarcinoma (MAC16) model, there are marked reduction in tumor size in animal fed with MCT
Coconut oil and MCT shows anticancer effect in mammary tumor incidence
Coconut oil and MCT shows cancer promoting effect of azoxymethane (AOM)-in rat colon tumors model
MCT-containing diet also prevent tumor formation in N-nitrosomethylurea animal mammary tumor model

Due to high fat and low carbohydrate composition it can be considered as a ketogenic diet (KD), consumption of which forces the body to burn fat rather than carbohydrate. Ketogenic diet reduces the frequency of epileptic seizures and includes treatment for several rare metabolic disorders. Several published articles have reported the anticancer effect of ketogenic diet.

Due to inefficiency of cancer cell in processing ketone bodies for energy, ketogenic diet are effective for cancer treatment. Consumption of ketogenic diet results in carbohydrate restriction and consequently decreases the serum glucose and insulin level followed by increase in lipolysis. Fatty acid activate the peroxisome proliferator-activated receptor α (PPAR α). PPAR α increase fatty acid oxidation and ketogenesis as well as inhibit fatty acid synthesis and glycolysis.

Both Insulin and IGF-1 activates the phosphatidylinositol-3 kinase (PI3K)–Akt–mammalian target of rapamycin complex 1 (mTORC1) signaling pathway. This pathway promotes sustained proliferative signaling, resisting cell death and modulates cellular mechanism which are the hall mark of cancer. Ketogenic diet means carbohydrate and protein restriction which results in drop of insulin level and less bioavailability of IGF-1 respectively. As a result (PI3K)–Akt–mTORC1 signaling pathway are not activated. mTORC1 also inhibit the PPAR α and downregulate ketogenesis. Interestingly ketogenic diet also modulates the cell signaling pathways, which are also the target of some anticancer drugs. Adding fresh coconut into daily dishes will be the non-toxic alternative cancer treatments.

It was reported long before that coconut oil is composed of fatty acids, sterols and cytokinins. Among sterol in coconut oil, beta-sitosterol is most abundant. Oral bioavailability of β -sitosterol is 36.9%. It inhibits proliferation and induces apoptosis in breast cancer cell MCF-7 and human leukemic U937 cells. It activates

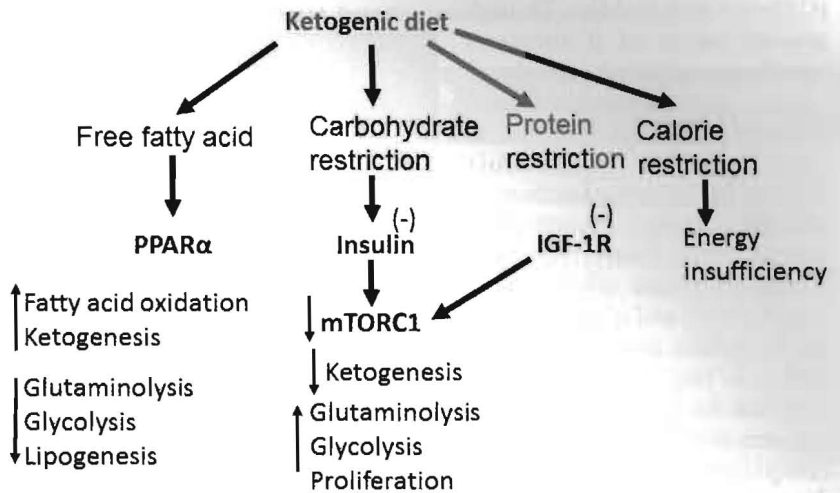


Fig 1: Anticancer role of ketogenic diet

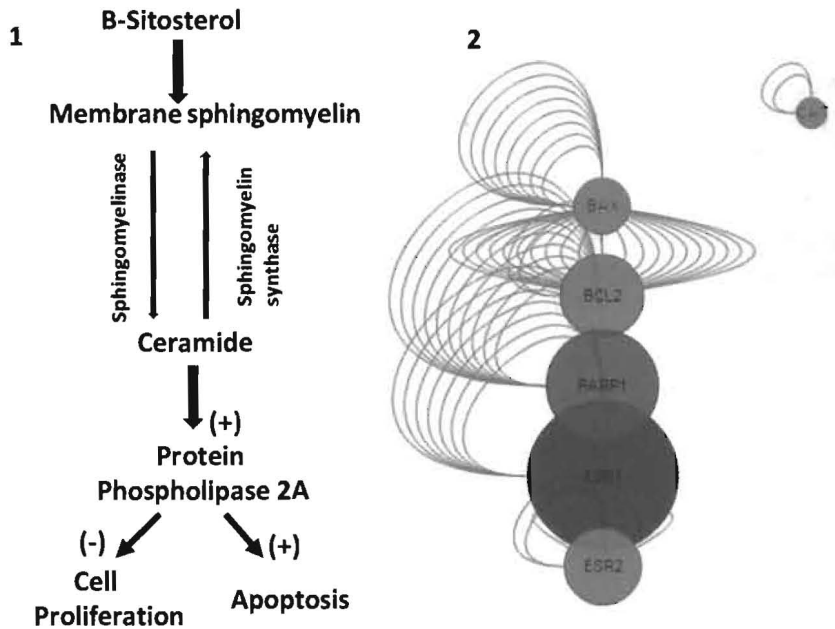


Fig. 2.1 Mechanism of anticancer activity of β -sitosterol.

2.2 Anticancer activity also reflected in interaction (from BioGRID) of β -sitosterol regulated gene.

caspase-3 and Bax/Bcl-2 ratio U937 cells.

Cytotoxicity of β -sitosterol against HT-29 cell line (colon carcinoma) has also been also reported. It shows inhibitory activity and IC₅₀ value in different cancer cell lines as follows (control: adriamycin, MCF-7, IC₅₀=1.5±0.2 μ M; K562, IC₅₀=0.07±0.01 μ M; Bowes, IC₅₀=0.45±0.01 μ M; T24S, IC₅₀=5.8±0.6 μ M; A549,

IC₅₀=15.8±6.7µM). Though several target of β sitosterol has been reported, its detail anticancer mechanism of action are yet to be explored. Delta (5)-avenasterol (fucosterol) inhibits rat lens aldose reductase (RLAR), human recombinant aldose reductase (HRAR), protein tyrosine phosphatase 1B (PTP1B), and α glucosidase. As it inhibits aldose reductase (AR), it may be a potential molecule for the management of diabetes and diabetes-associated complications. Fucosterol decreased activity of PTPN1 protein and its role in cancer is yet to be explored.

Some cytokinins and its derivatives reportedly retard and reduce tumor growth. Coconut water contains a large spectrum of cytokinin and some of them are potential anticancer agents (Table 2). Selective killing of cancer cell is still a greatest challenge and needs to be addressed. Research shows Kinetin riboside (KR) have cancer specific cytotoxicity. KR is present in coconut milk in nanomole level. KR selectively inhibits the proliferation of cancer cells and induces apoptosis. In KR exposed cell, proapoptotic Bax are upregulated and anti-apoptotic Bcl-2 protein are downregulated. Besides, this increases the Cytochrome c level along with procaspase 9 and its active form in KR treated cell may be the underlining cause of anticancer activity. Another isoprenoid cytokinins, N6-isopentenyladenine present in coconut water shows anticancer activity in cell culture based assay. Cytokinin N6-isopentenyladenosine (I6A) (IC₅₀= 12.2 mM) also inhibits the growth of human breast cancer MCF-7 cells. I6A induces apoptosis in MCF-7 cells by inhibiting the Akt activation and suppresses the nuclear factor kappaB (NF-κB) pathway. I6A also induces apoptosis in colon cancer cell line through the phosphorylation of c-jun N-terminal kinase (JNK) and consequent phosphorylation of c-jun. Anticancer role of N6-Benzylaminopurine (6-BAP) and its derivatives has been reported by several articles. 6-BAP activates protein kinase A (PKA) and stimulates melanogenesis. Melanin pigments prevent skin photocarcinogenesis. Another cytokinin, Kinetin modulates aberrant neurofibromatosis type 1 (NF1) pre-

Table 2: Anticancer effect of sterol and other compounds isolated from VCO and coconut water.

Sterol	Disease	
	Therapeutic (Reported)	Therapeutic(Predicted)
β-sitosterol	Anticancer	
Delta (5)-avenasterol	Diabetes Complications	Mediastinal Neoplasms, Lymphoma
Stigmasterol	Anticancer	
Other compounds		
Gamma-tocotrienol	Anticancer	
Oleic acid	Anticancer	

Table 3: Anticancer effect of cytokinins present in coconut water.

Cytokinin in coconut water	Therapeutic (Reported)
N6-isopentenyladenosine	Anticancer
N6-Isopentenyladenine	Anticancer
N6 -benzyladenine or N6-Benzylaminopurine	Anticancer
N6 -benzyladenosine	Anticancer
kinetin	Anticancer
kinetin riboside	Anticancer
Trans-Zeatin	Anticancer
Trans-zeatin riboside	Anticancer
Cn-AMP2 Peptide	Anticancer: 1321N1 and U87MG human glioma cell lines

mRNA, IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) and other genes splicing and improve exon inclusion and may play a role in cancer prevention.

Trans-Zeatin inhibit UVB-induced MMP-1 expression and may have anticancer role. The latest addition is anionic peptide Cn-AMP2 (TESYFVFSVGM) which was isolated from coconut water and it inhibits the proliferation of 1321N1 (IC₅₀=1.25 mM) and U87MG (IC₅₀=1.85 mM) human glioma cell lines. Cn-AMP2 has anticancer activity against human glioblastoma and may be used for treatment against other cancers.

These results highlight the previously unnoticed link between coconut products and its promising anticancer effects. It also indicates the possible other therapeutic potential of cytokinin. We are unable to analyze the pathways and diseases enrichment for Trans-Zeatin, Trans-zeatin riboside, benzyladenosine due to insufficient information. Based on accumulating information, it is clear that the beneficial effects of some cytokinins are yet to be explored. Incorporating this modern knowledge into design the novel treatment could be effective in combating cancer and other diseases.

T pathways and diseases enrichment analyses for 5 cytokinins (kinetin riboside, kinetin, isopentenyladenosine, Isopentenyladenine, Benzylaminopurine) were performed and the results are following

Cytokinins	Enriched pathways	Enriched diseases	Disease categories
kinetin riboside	Cell cycle, p53 signaling pathway, Cellular responses to stress, Small cell lung cancer, Prostate cancer, Mitotic M-M/G1 phases, Disease, Apoptosis, Metabolism, Signal Transduction	Neoplasms by Histologic Type, Neoplasms, Hemic and Lymphatic Diseases, Skin Diseases, Skin and Connective Tissue Diseases, Neoplasms, Connective Tissue, Immunoproliferative Disorders, Sarcoma, Lymphoproliferative Disorders, Osteosarcoma, Neoplasms, Connective and Soft Tissue	Cancer, Skin disease, Connective tissue disease, Immune system disease, Lymphatic disease, Cardiovascular disease
kinetin			
isopentenyladenosine			
Isopentenyladenine			
Benzylaminopurine			

References

- Lim Sylianco C.Y., Anticarcinogenic effects of coconut oil. Phillip. J. Coconut Studies, 1987 12 (2) 89-102. 65. Cohen L. A., Thompson D. O., Maeura, Choi K., Blank M. E., Rose D. P., Dietary fat and mammary cancer.
- Promoting effects of different dietary fats on N-nitrosomethylurea-induced rat mammary tumorigenesis. J. Natl. Cancer Inst., 1986 77 (1) 33-42.
- Stafford P, Abdelwahab MG, Kim do Y, Preul MC, Rho JM, Scheck AC. The ketogenic diet reverses gene expression patterns and reduces reactive oxygen species levels when used as an adjuvant therapy for glioma. Nutr Metab (Lond). 2010 Sep 10;7:74.
- Otto C, Kaemmerer U, Illert B, Muehling B, Pfetzer N, Wittig R, Voelker HU, Thiede A, Coy JF. Growth of human gastric cancer cells in nude mice is delayed by a ketogenic diet supplemented with omega-3 fatty acids and medium-chain triglycerides. BMC Cancer. 2008 Apr 30;8:122.
- Chen FM, Wang JY, Sun LC, Juang RF, Huang TJ, Hsieh JS. Efficacy of medium-chain triglycerides compared with long-chain triglycerides in total parenteral nutrition in patients with digestive tract cancer undergoing surgery. Kaohsiung J Med Sci. 2005 Nov;21(11):487-94.
- Wolters U, Keller HW, Becker R, Stickeler P, Dahlmeyer M, Müller JM. Influence of various fatty acids on tumour growth in total parenteral nutrition. Eur Surg Res. 1994;26(5):288-97.
- Kimoto Y, Tanji Y, Taguchi T, Sugimoto T, Watanabe T, Tsukamoto F, Kim S, Yoneda K, Takamura Y, Izukura M, Shiba E, Takai S. Antitumor effect of medium-chain triglyceride and its influence on the self-defense system of the body. Cancer Detect Prev. 1998;22(3):219-24.
- Tisdale MJ, Brennan RA. A comparison of long-chain triglycerides and medium-chain triglycerides on weight loss and tumour size in a cachexia model. Br J Cancer. 1988 Nov;58(5):580-3.
- Craig-Schmidt M, White MT, Teer P, Johnson J, Lane HW. Menhaden, coconut, and corn oils and mammary tumor incidence in BALB/c virgin female mice treated with DMBA. Nutr Cancer. 1993;20(2):99-106.
- Reddy BS, Maeura Y. Tumor promotion by dietary fat in azoxymethane-induced colon carcinogenesis in female F344 rats: influence of amount and source of dietary fat. J Natl Cancer Inst. 1984 Mar;72(3):745-50.
- Cohen LA, Thompson DO. The influence of dietary medium chain triglycerides on rat mammary tumor development. Lipids. 1987 Jun;22(6):455-61.
- Cohen LA, Thompson DO, Maeura Y, Weisburger JH. Influence of dietary medium-chain triglycerides on the development of N-methylnitrosourea-induced rat mammary tumors. Cancer Res. 1984 Nov;44(11):5023-8.
- Cullingford, T. E. (2004). The ketogenic diet; fatty acids, fatty acid activated receptors and neurological disorders. Prostaglandins, Leukotrienes and Essential Fatty Acids, 70, 253–264.
- Cullingford TE. The ketogenic diet; fatty acids, fatty acid-activated receptors and neurological disorders. Prostaglandins Leukot Essent Fatty Acids. 2004 Mar;70(3):253-64.
- Klement RJ, Champ CE. Calories, carbohydrates, and cancer therapy with radiation: exploiting the five R's through dietary manipulation. Cancer Metastasis Rev. 2014 Mar;33(1):217-29.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646-74.
- Sengupta S, Peterson TR, Laplante M, Oh

- S, Sabatini DM. mTORC1 controls fasting-induced ketogenesis and its modulation by ageing. *Nature*. 2010 Dec 23;468(7327):1100-4.
18. Chai JW, Kuppusamy UR, Kanthimathi MS. Beta-sitosterol induces apoptosis in MCF-7 cells. *Malays J Biochem Molecular Bio*. 2008;16:28-30.
19. Park C, Moon DO, Rhu CH, Choi BT, Lee WH, Kim GY, Choi YH. β -sitosterol induces antiproliferation and apoptosis in human leukemic U937 cells through activation of caspase-3 and induction of Bax/Bcl-2 ratio. *Biol Pharm Bull*. 2007;30:1317-23.
20. Saeidnia S, Manayi A, Ahmad R, Gohari A. R., Abdollahi M. The Story of Beta-sitosterol- A Review. *European Journal of Medicinal Plants*, 4(5): 590-609, 2014.
21. Manayi A, Saeidnia S, Ostad SN, Hadjiakhoondi A, Ardekani MR, Vazirian M, Akhtar Y, Khanavi M. Chemical constituents and cytotoxic effect of the main compounds of *Lythrum salicaria* L. *Z Naturforsch C*. 2013 Sep-Oct;68(9-10):367-75.
22. Song W, Jin R, Liu J. Studies on the chemical constituents of stems of *Erycibe schmidtii* Craib[J]. *China journal of Chinese materia medica*, 1997, 22(6): 359-360.
23. Zhou, J., Xie, G. and Xinjian, Y. (2012) Anticancer active components in TCM. TCM series of active components. Science Press, Bei Jing.
24. Jung HA, Islam MN, Lee CM, Oh SH, Lee S, Jung JH, Choi JS. Kinetics and molecular docking studies of an anti-diabetic complication inhibitor fucosterol from edible brown algae *Eisenia bicyclis* and *Ecklonia stolonifera*. *Chem Biol Interact*. 2013 Oct 25;206(1):55-62.
25. Casati S, Ottria R, Baldoli E, Lopez E, Maier JA, Ciuffreda P. Effects of cytokinins, cytokinin ribosides and their analogs on the viability of normal and neoplastic human cells. *Anticancer Res*. 2011 Oct;31(10):3401-6.
26. Dudzik P, Dulińska-Litewka J, Wyszko E, Jędrychowska P, Opałka M, Barciszewski J, Laidler P. Effects of kinetin riboside on proliferation and proapoptotic activities in human normal and cancer cell lines. *J Cell Biochem*. 2011 Aug;112(8):2115-24.
27. Griffaut B, Bos R, Maurizis JC, Madelmont JC, Ledoigt G. Cytotoxic effects of kinetin riboside on mouse, human and plant tumour cells. *Int J Biol Macromol*. 2004 Aug;34(4):271-5.
28. Ge L, Yong JW, Tan SN, Yang XH, Ong ES. Analysis of some cytokinins in coconut (*Cocos nucifera* L.) water by micellar electrokinetic capillary chromatography after solid-phase extraction. *J Chromatogr A*. 2004 Sep 3;1048(1):119-26.
29. Yong JW, Ge L, Ng YF, Tan SN. The chemical composition and biological properties of coconut (*Cocos nucifera* L.) water. *Molecules*. 2009 Dec 9;14(12):5144-64.
30. Naito A, Suzuki A, Ueda S, Nomoto H, Toriyama-Baba H, Asamoto M, Tsuda H. Preferential mammary carcinogenic effects of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in human c-Ha-ras proto-oncogene transgenic rats. *Cancer Sci*. 2004 May;95(5):399-403.
31. Plentz R, Park JS, Rhim AD, Abravanel D, Hezel AF, Sharma SV, Gurumurthy S, Deshpande V, Kenific C, Settleman J, Majumder PK, Stanger BZ, Bardeesy N. Inhibition of gamma-secretase activity inhibits tumor progression in a mouse model of pancreatic ductal adenocarcinoma. *Gastroenterology*. 2009 May;136(5):1741-9.e6.
32. Moon HJ, Finney J, Xu L, Moore D, Welch DR, Mure M. MCF-7 cells expressing nuclear associated lysyl oxidase-like 2 (LOXL2) exhibit an epithelial-to-mesenchymal transition (EMT) phenotype and are highly invasive in vitro. *J Biol Chem*. 2013 Oct 18;288(42):30000-8.
33. Grudzien P, Lo S, Albain KS, Robinson P, Rajan P, Strack PR, Golde TE, Miele L, Foreman KE. Inhibition of Notch signaling reduces the stem-like population of breast cancer cells and prevents mammosphere formation. *Anticancer Res*. 2010 Oct;30(10):3853-67.
34. Rajabi M, Signorelli P, Gorincioi E, Ghidoni R, Santaniello E. Antiproliferative activity of N6-isopentenyladenosine on MCF-7 breast cancer cells: cell cycle analysis and DNA-binding study. *DNA Cell Biol*. 2010 Nov;29(11):687-91.
35. Laezza C, Malfitano AM, Di Matola T, Ricchi P, Bifulco M. Involvement of Akt/NF- κ B pathway in N6-isopentenyladenosine-induced apoptosis in human breast cancer cells. *Mol Carcinog*. 2010 Oct;49(10):892-901.
36. Casati S, Ottria R, Baldoli E, Lopez E, Maier JA, Ciuffreda P. Effects of cytokinins, cytokinin ribosides and their analogs on the viability of normal and neoplastic human cells. *Anticancer Res*. 2011 Oct;31(10):3401-6.
37. Laezza C, Caruso MG, Gentile T, Notarnicola M, Malfitano AM, Di Matola T, Messa C, Gazzo P, Bifulco M. N6-isopentenyladenosine inhibits cell proliferation and induces apoptosis in a human colon cancer cell line DLD1. *Int J Cancer*. 2009 Mar 15;124(6):1322-9.
38. Kim S, Lee J, Jung E, Lee J, Huh S, Hwang

- H, Kim Y, Park D. 6-Benzylaminopurine stimulates melanogenesis via cAMP-independent activation of protein kinase A. *Arch Dermatol Res.* 2009 Mar;301(3):253-8.
39. Tan, S.N.; Yong, J.W.H.; Ge, L. Analyses of Phytohormones in Coconut (*Cocos Nucifera* L.) Water Using Capillary Electrophoresis-Tandem Mass Spectrometry. *Chromatography* 2014, 1, 211-226.
40. Ge L, Yong JW, Tan SN, Yang XH, Ong ES. Analysis of some cytokinins in coconut (*Cocos nucifera* L.) water by micellar electrokinetic capillary chromatography after solid-phase extraction. *J Chromatogr A.* 2004 Sep 3;1048(1):119-26.
41. Dvořák Z, Starha P, Trávníček Z. Evaluation of in vitro cytotoxicity of 6-benzylaminopurine carboplatin derivatives against human cancer cell lines and primary human hepatocytes. *Toxicol In Vitro.* 2011 Apr;25(3):652-6.
42. Spitali P, Aartsma-Rus A. Splice modulating therapies for human disease. *Cell.* 2012 Mar 16;148(6):1085-8.
43. Pros E, Fernández-Rodríguez J, Benito L, Ravello A, Capellá G, Blanco I, Serra E, Lázaro C. Modulation of aberrant NF1 pre-mRNA splicing by kinetin treatment. *Eur J Hum Genet.* 2010 May;18(5):614-7.
44. Hims MM, Ibrahim EC, Leyne M, Mull J, Liu L, Lazaro C, Shetty RS, Gill S, Gusella JF, Reed R, Slaugenhaupt SA. Therapeutic potential and mechanism of kinetin as a treatment for the human splicing disease familial dysautonomia. *J Mol Med (Berl).* 2007 Feb;85(2):149-61.
45. Yang B, Ji C, Kang J, Chen W, Bi Z, Wan Y. Trans-Zeatin inhibits UVB-induced matrix metalloproteinase-1 expression via MAP kinase signaling in human skin fibroblasts. *Int J Mol Med.* 2009 Apr;23(4):555-60.
46. Prabhu S, Dennison SR, Mura M, Lea RW, Snape TJ, Harris F. Cn-AMP2 from green coconut water is an anionic anticancer peptide. *J Pept Sci.* 2014 Dec;20(12):909-15. ■