Journal of Pharmacognosy and Phytochemistry
Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
www.phytojournal.com
JPP 2024; 13(2): 722-727
Received: 06-02-2024
Accepted: 04-03-2024

Sarah Rangnekar
Trinity College of Pharmacy, Pune, Maharashtra, India

Pooja Sutar
Trinity College of Pharmacy, Pune, Maharashtra, India

Corresponding Author:
Sarah Rangnekar
Trinity College of Pharmacy, Pune, Maharashtra, India

Dionaea muscipula solander ex ellis (Venus Flytrap)

Sarah Rangnekar and Pooja Sutar

DOI: https://doi.org/10.22271/phyto.2024.v13.i2e.14916

Abstract
The species of *Dionaea muscipula* solander ex ellis is considered as a carnivorous species and thus the medical aspect of this category of plants is not explored or studied in a detailed manner. However these plants appear to contain a variety of secondary metabolites which are bioactive in nature and the purpose of this review article is to explore the therapeutic potential and the nature of these metabolites and their molecular mechanism.

Keywords: *Dionea muscipula*, cytostatic, anticarcinogenic, apoptosis

Introduction

About Plant

This type of plant has been used by different communities in respect to the traditional medicine system for many years. *Dionaea muscipula* was actively a subject for modern biomedical research and their study stated that the components or the secondary metabolite present in this category contained exceptionally interesting therapeutic properties. Below stated are the different metabolites and their therapeutic properties

Secondary Metabolite (St Class ET) Plumbagin

Naphthoquinones

It has broad-range activity: Phytotoxic, insecticidal and antibacterial. It also possesses cytostatic and anticarcinogenic properties.

Plumbagin

This phytoconstituent of the plant possesses anticancer, anti-inflammatory, antifungal and antibacterial properties. This component is yellow in color. The main mechanism of Plumbagin is that it inhibits the enzyme topoisomerase II which is present in HL 60 cells. It also interacts directly with the tubulin at the colchicine binding site, thus disrupting the micro tubular network. Plumbagin also inhibits the nuclear factor kappa B signaling pathway which is induced by carcinogens. The expression of the anti-apoptotic gene which is mainly Bcl-xl is blocked. In the condition of melanoma cell cycle arrest is induced in the G2/M phase leading to apoptosis. The activation of JNK and ERK can be seen.

Polyphenolic compound

The polyphenolic compounds are chemical compounds which contain at least one aromatic ring with one or several hydroxyl substitutions. In plants the phenolic compounds are the secondary plant metabolites which are synthesized by phenylpropanoid metabolism.

Ellagic acid

This phytoconstituent possesses chemo preventive property. It reduces proliferation of cells and it binds to DNA transcription factor which results in inhibition of NF-kB. Ellagic acid activate caspase-3 and releases the cytochrome C which result in apoptosis of cancer cell in pancreatic cancer.

Gallic acid

This phytoconstituent possessing anti-cancer properties is secreted by the aerial parts of the plant. The gallic acid is responsible for the arrest of cell cycle (Human leukemia cells) by reducing the E levels and cyclin D. The Gallic acid also results in apoptosis resulting in decrease in the cellular number. Cyclooxygenase 2 which is related directly to progression of the cancer is also inhibited by this constituent.

Vanillin

I the production of vanillin is done by biotechnological or chemical technique which involves utilization of specific bacteria or fungi.

Vanillin is responsible for inhibition in relation to the growth and development of adenocarcinoma cell line (category: Mammary type: 4T1). Vanillin also reduces activity of MMP-9 (matrix metalloproteinase-9) which results in cell invasion and migration reduction thus providing an anticancer property.

Protocatechuic acid

It is a poly phenolic compound that shows therapeutic action against several diseases. Protocatechuic acid impedes the cell proliferation and migration of human gastric adenocarcinoma at atoxic concentration. The modulation of Ras/Akt cascade pathway, RhoB/protein kinase CE and inhibition of NF-kB pathway and MMP-2 expression results in the demonstration of anticancer property.

Caffeic acid

Caffeic acid enhances ROS level thus inducing oxidation responsible for alteration of DNA and it is responsible for alteration of potential of membrane of mitochondria in case of (HT-1080) fibro sarcoma cells of Homosapiens. Caffeic acid is responsible for apoptosis of cancer cells. It is responsible for inhibition of methylation of DNA by inhibiting DNA methyltransferase.

Caffeic acid is the most potent anti-proliferation agent on T47D human breast cancer cells.

Chlorogenic acid

Chlorogenic acid reduces the proliferation rate of Human adenocarcinoma Caco-2 cells. It also induces apoptosis in human leukemia cells by generating ROS and decreasing membrane potential of mitochondria. Chlorogenic acid also causes damage to the DNA in A549 lung cancer cells.

Ferulic acid

Ferulic acid causes inhibition of lipid membrane peroxidation and reduces formation of break in DNA strands resulting from free radical thus responsible for the protection of DNA against the gamma-radiation.

Salicylic acid

Salicylic acid under normal oxygen level shows no effect on proliferation of colon carcinoma cells (CaCo-2) but it reduces proliferation of cells under hypoxia. Salicylic acid also results in no changes in phosphorylation of ERK1/2 under normal oxygen level.

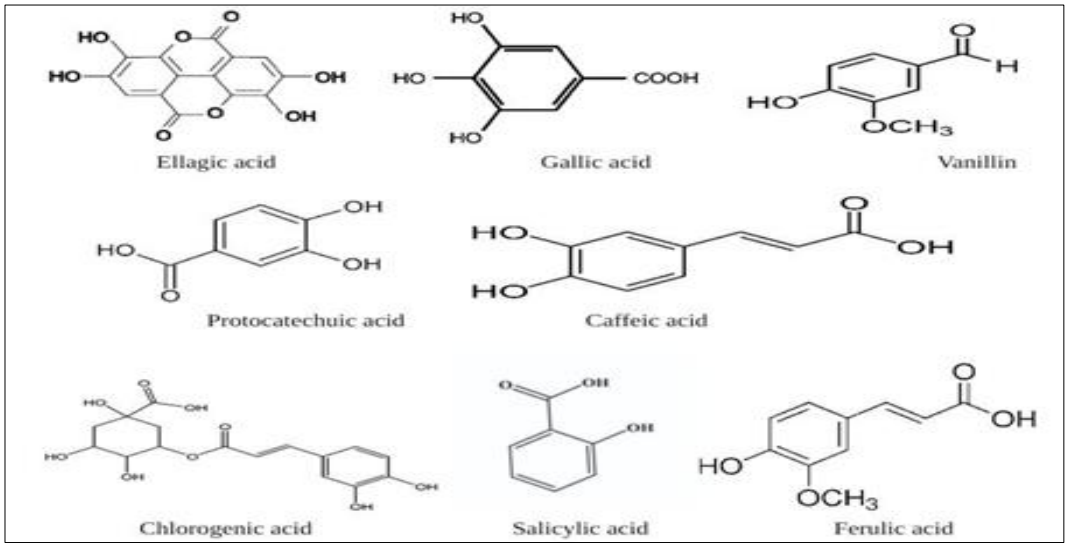

Fig 1: Structure of Phenolic compounds

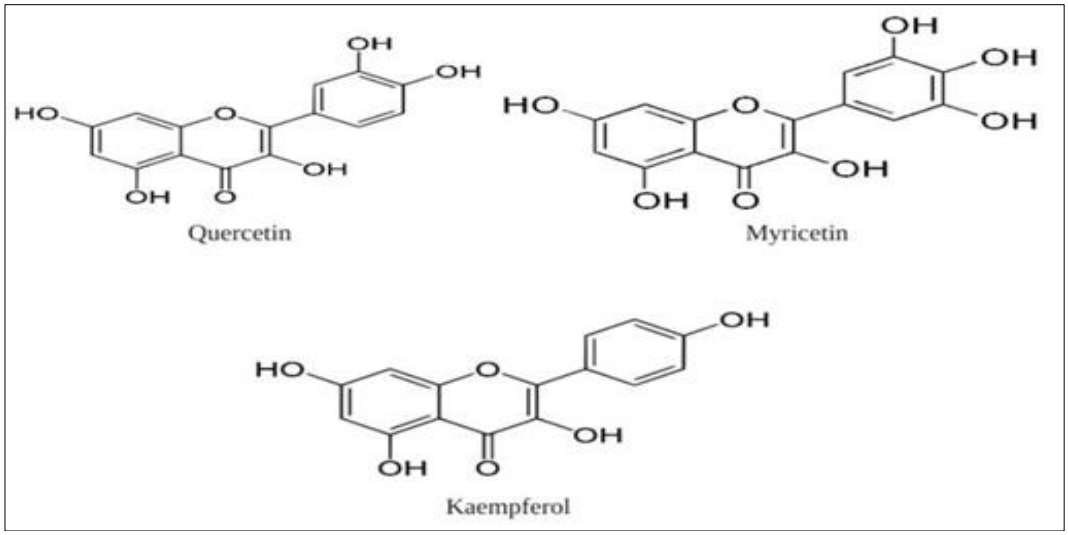

Fig 2: Structure of flavonoids

Flavonoids

Quercetin

Quercetin demonstrates its anti-proliferation property by inhibition of the G2/M phase in cell cycle. Quercetin is responsible for reduction in SW480 colon cancer cells through inhibition of the Wnt pathway transcriptional activity resulting from reduction in the level of beta-catenin pathway which demonstrate its apoptotic property.

Myricetin

Myricetin is responsible for inhibition of mutagenesis which is caused by carcinogenic agent for example benzbenzo (a) pyrene. Myricetin also cause apoptosis through the activation of caspase-3 and caspase-9 which result in cancer cell apoptosis. Myricetin activate the caspase-3 after cleavage of DNA and through cdc2 and cycling B12 down regulation which result in human bladder carcinoma T4 cell line apoptosis.

Kaempferol

It is responsible for inhibiting the proliferation of cancer oral cells such as SCC-25 and SCC-1483 at 40 microM concentration. Kaempferol also demonstrates inhibition of ovarian cancer and is responsible for apoptosis through cell death.

Experiments

Testing anticancer properties of phytoconstituent

- Plumbagin inhibited mice tumor (wild type) by inhibition of PKCe, Stat3, AKT activation in mice model.
- With the administration of gallic acid in mice reduction in metastasis progression is recorded. Inhibition of growth and progression of prostate cancer is observed when gallic acid is induced in the mouse prostate TRAMP model.
- Decreased in levels of Cdk6, Cdk4, and Cdk2 and decrease in number of cyclin B1 and E recorded during Western-blot test where the specimen was mice prostate U-2OS and MNNG/HOS which are human osteosarcoma cell lines when administered with gallic acid the cell proliferation is inhibited.
- *In vivo* experiments were conducted on rat models which were induced with colon cancer to portray its chemo preventive activity. It was recorded that ellagic acid decreases the level of NF-kB.
- *In vivo* experiments were conducted where the specimen were BBLB/c treated mice, whose mammary adenocarcinoma cells where injected with vanillin to portray its anticancer effect. It was recorded that vanillin causes reduction in the colonies formed in lung metastasis condition.
- Experiment was conducted using a mice model to portray the anti-metastasis activity of the protocatechuic acid and the experiment successfully determined the anticancer property.
- Experiments determine apoptosis occurring by the Fas/FasL pathway. Inhibition of CYP1A1 which is an aryl hydrocarbon receptor-induced gene expression is recorded.
- Ferulic acid administered through an oral route in Sprague-rat previously treated with 7, 12-dimethylbenz (a) anthracene (DMBA) is responsible for reduction in tumor cell formation.
- Quercetin is responsible for cell death by activating of caspases 3 and caspases 9 which result in hepatocellular carcinoma cell apoptosis.
- Experiments conducted on mice model show that myricetin is responsible for inhibiting the T-24 xenograft growth.

Conclusion

The above paper demonstrates the anticancer properties and activities of the *Dionea muscipula* solander ex ellis (Venus Flytrap). The paper summarizes the action of different phytoconstituents, their nature of action and their anticancer activities.

References

1. Baguley BC. Multiple drug resistance mechanisms in cancer. Mol Biotechnol. 2010 Sep;46(3):308-16. DOI: 10.1007/s12033-010-9321-2.
2. Morens DM, Fauci AS. Emerging infectious diseases in 2012, 20 years after the institute of medicine report. MBio. 2012 Nov 6;3(6). DOI: 10.1128/mBio.00494-12.
3. Liu FS. Mechanisms of chemotherapeutic drug resistance in cancer therapy - a quick review. Taiwan J Obstet Gynecol. 2009 Sep;48(3):239-44. DOI: 10.1016/S1028-4559(09)60296-5.
4. Cragg GM, Newman DJ. Natural products: A continuing source of novel drug leads. Biochim Biophys Acta. 2013 Nov;1830(6):3670-95. DOI: 10.1016/j.bbagen.2013.02.008.
5. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod. 2012 Feb 24;75(3):311-35. DOI: 10.1021/np200906s.
6. Bourgaud F, Gravot A, Milesi S, Gontier E. Production of plant secondary metabolites: A historical perspective. Plant Sci. 2001 Nov 29;161(5):839-51. DOI: 10.1016/S0168-9452(01)00490-3.
7. Craik DJ. Host-defense activities of cyclotides. Toxins. 2012 Feb;4(2):139-56. DOI: 10.3390/toxins4020139.
8. Hartmann T. From waste products to Eco chemicals: Fifty years research of plant secondary metabolism. Phytochemistry. 2007 Nov;68(22-24):2831-46. DOI: 10.1016/j.phytochem.2007.09.017.
9. Heinen TE, da Veiga AB. Arthropod venoms and cancer. Toxicon. 2011 Apr 1;57(4):497-511. DOI: 10.1016/j.toxicon.2011.01.002.
10. Jain D, Kumar S. Snake venom: A potent anticancer agent. Asian Pac J Cancer Prev. 2012;13(10):4855-60. PMID: 23244135.
11. Namdeo A. Plant cell elicitation for production of secondary metabolites: A review. Phcog Rev. 2007;1:69-79.
12. Schmidt EW, Donia MS, McIntosh JA, Fricke WF, Ravel J. Origin and variation of tunicate secondary metabolites. J Nat Prod. 2012;75:295-304. DOI: 10.1021/np200665k.
13. Amin AR, Kucuk O, Khuri FR, Shin DM. Perspectives for cancer prevention with natural compounds. J Clin Oncol. 2009;27:2712-25. DOI: 10.1200/JCO.2008.20.6235.
14. Kreher B, Neszmélyi A, Wagner H. Naphthoquinones from *Dionaea muscipula*. Phytochemistry. 1990;29:605-6. DOI: 10.1016/0031-9422(90)85125-Y.
15. Gaascht F, Teiten MH, Schumacher M, Dicato M, Diederich M. Approche végétale dans le traitement des leucémies. Corresp Onco-Hématol. 2010;V:102-8.

16. Gullett NP, Ruhul Amin AR, Bayraktar S, Pezzuto JM, Shin DM, Khuri FR, *et al*. Cancer prevention with natural compounds. Semin Oncol. 2010;37:258-81. DOI: 10.1053/j.seminoncol.2010.06.014.
17. Surh YJ. Cancer chemoprevention with dietary phytochemicals. Nat Rev Cancer. 2003;3:768-80. DOI: 10.1038/nrc1189.
18. Schumacher M, Kelkel M, Dicato M, Diederich M. Gold from the sea: Marine compounds as inhibitors of the hallmarks of cancer. Biotechnol Adv. 2011;29:531-47. DOI: 10.1016/j.biotechadv.2011.02.002.
19. Teiten MH, Gaascht F, Dicato M, Diederich M. Targeting the wingless signaling pathway with natural compounds as chemopreventive or chemotherapeutic agents. Curr Pharm Biotechnol. 2012;13:245-54. DOI: 10.2174/138920112798868593.
20. Kelkel M, Jacob C, Dicato M, Diederich M. Potential of the dietary antioxidants resveratrol and curcumin in prevention and treatment of hematologic malignancies. Molecules. 2010;15:7035-74. DOI: 10.3390/molecules15107035.
21. Bishayee A, Politis T, Darvesh AS. Resveratrol in the chemoprevention and treatment of hepatocellular carcinoma. Cancer Treat Rev. 2010;36:43-53. DOI: 10.1016/j.ctrv.2009.10.002.
22. Kraft TE, Parisotto D, Schempp C, Efferth T. Fighting cancer with red wine? Molecular mechanisms of resveratrol. Crit Rev Food Sci Nutr. 2009;49:782-99. DOI: 10.1080/10408390802248627.
23. Martin MA, Goya L, Ramos S. Potential for preventive effects of cocoa and cocoa polyphenols in cancer. Food Chem Toxicol. 2013;56:336-51. DOI: 10.1016/j.fct.2013.02.020.
24. Maskarinec G. Cancer protective properties of cocoa: A review of the epidemiologic evidence. Nutr Cancer. 2009;61:573-9. DOI: 10.1080/01635580902825662.
25. Khalil MI, Sulaiman SA. The potential role of honey and its polyphenols in preventing heart diseases: A review. Afri J Tradit Complement Altern Med. 2010;7:315-21.
26. Sawadogo WR, Schumacher M, Teiten MH, Dicato M, Diederich M. Traditional West African pharmacopeia, plants and derived compounds for cancer therapy. Biochem Pharmacol. 2012;84:1225-40. DOI: 10.1016/j.bcp.2012.07.021.
27. Nobili S, Lippi D, Witort E, Donnini M, Bausi L, Mini E, *et al*. Natural compounds for cancer treatment and prevention. Pharmacol Res. 2009;59:365-78. DOI: 10.1016/j.phrs.2009.01.017.
28. Orlikova B, Diederich M. Power from the garden: plant compounds as inhibitors of the hallmarks of cancer. Curr Med Chem. 2012;19:2061-87. DOI: 10.2174/092986712800228998.
29. Efferth T, Li PC, Konkimalla VS, Kaina B. From traditional Chinese medicine to rational cancer therapy. Trends Mol Med. 2007;13:353-61. DOI: 10.1016/j.molmed.2007.07.001.
30. Folmer F, Jaspars M, Dicato M, Diederich M. Marine natural products as targeted modulators of the transcription factor NF-kappaB. Biochem Pharmacol. 2008;75:603-17. DOI: 10.1016/j.bcp.2007.07.044.
31. Senevirathne M, Kim SK. Utilization of seafood processing by-products: Medicinal applications. Adv Food Nutr Res. 2012;65:495-512. DOI: 10.1016/B978-0-12-416003-3.00032-9.
32. Zhou ZF, Guo YW. Bioactive natural products from Chinese marine flora and fauna. Acta Pharmacol Sin. 2012;33:1159-69. DOI: 10.1038/aps.2012.110.
33. Mayer AM, Gustafson KR. Marine pharmacology in 2005-2006: Antitumour and cytotoxic compounds. Eur J Cancer. 2008;44:2357-87. DOI: 10.1016/j.ejca.2008.07.001.
34. Remington JP. The Dispensatory of the United States of America. Philadelphia: Lippincott; 1918. 2010 p.
35. Muhammad A, Analco GJA, Martineau LC, Musallam L, Madiraju P, Nachar A, *et al*. Antidiabetic compounds from Sarracenia purpurea used traditionally by the Eeyou Istchee Cree First Nation. J Nat Prod. 2012;75:1284-8. DOI: 10.1021/np3001317.
36. Renshaw CJ. Treatment of small-pox by Sarracenia Purpurea. BMJ. 1863;1:127-127. DOI: 10.1136/bmj.1.109.127.
37. Behera KK, Sahoo S, Mohapatra PC. Medicinal plant resources for bio prospecting and drug development in tribal rich district of Orissa, India. Ethnobot Leafl. 2007;11:106-12.
38. Kayang H, Kharbuli B, Myrboh B, Syiem D. Medicinal plants of Khasi hills of Meghalaya, India. In: Bernáth ENJ, Craker LE, Gardner ZE, editors. III WOCMAP Congress on Medicinal and Aromatic Plants-Volume 1: Bio prospecting and Ethno pharmacology. Chiang Mai: Acta Horticulturae; c2003. p. 75-80.
39. Kumar S. The Medicinal Plants of North-East India. Jodhpur: Scientific Publishers; c2002. p. 212.
40. Prasad MNV, Jeeva S. Coal mining and its leachate are potential threats to Nepenthes *Khasiana Hook* F. (Nepenthaceae) that preys on insects-an endemic plant in North Eastern India. Biol Div Con. 2009;2:29-33.
41. Singh J, Mudgal V. Studies on habitat conditions of a few plants species of medicinal values of Nokrek Biosphere Reserve, Meghalaya. J Non-Timber for Products. 1999;6:4.
42. Volkov AG, Murphy VA, Clemmons JI, Curley MJ, Markin VS. Energetics and forces of the *Dionaea muscipula* trap closing. J Plant Physiol. 2012;169:55-64. DOI: 10.1016/j.jplph.2011.08.003.
43. Volkov AG, Harris SL, Vilfranc CL, Murphy VA, Wooten JD, Paulicin H, *et al*. Venus flytrap biomechanics: Forces in the *Dionaea muscipula* trap. J Plant Physiol. 2013;170:25-32. DOI: 10.1016/j.jplph.2012.08.009.
44. Volkov AG, Adesina T, Markin VS, Jovanov E. Kinetics and mechanism of *Dionaea muscipula* trap closing. Plant Physiol. 2008;146:694-702. DOI: 10.1104/pp.107.108241.
45. Schulze WX, Sanggaard KW, Kreuzer I, Knudsen AD, Bemm F, Thogersen IB, *et al*. The protein composition of the digestive fluid from the Venus flytrap sheds light on prey digestion mechanisms. Mol Cell Proteomics. 2012;11:1306-19. DOI: 10.1074/mcp.M112.021006.
46. Adlassnig W, Peroutka KM, Bauer S, Koshkin E, Lendl T, Lichtscheidl IK. Endocytotic uptake of nutrients in carnivorous plants. Plant J. 2012;71:303-13. DOI: 10.1111/j.1365-313X.2012.04997.x.
47. Krol E, Plachno BJ, Adamec L, Stolarz M, Dziubinska H, Trebacz K. Quite a few reasons for calling carnivores 'the most wonderful plants in the world.' Ann Bot (Lond). 2012;109:47-64. DOI: 10.1093/aob/mcr249.

48. Scala J, Iott K, Schwab DW, Semersky FE. Digestive secretion of *Dionaea muscipula* (Venus's Flytrap). Plant Physiol. 1969;44:367-71. DOI: 10.1104/pp.44.3.367.
49. Kovacik J, Klejdus B, Repcakova K. Phenolic metabolites in carnivorous plants: Inter-specific comparison and physiological studies. Plant Physiol Biochem. 2012;52:21-7. DOI: 10.1016/j.plaphy.2011.11.007.
50. Krolicka A, Szpitter A, Gilgenast E, Romanik G, Kaminski M, Lojkowska E. Induction of naphthoquinone and flavonoid production in *Dionaea muscipula* and Drosera capensis. Planta Med. 2006;72:137.
51. Nagata T, Ebizuka Y. Medicinal and Aromatic Plants XII. Dordrecht: Springer; c2002. p. 348.
52. Pakulski G, Budzianowski J. Ellagic acid derivatives and naphthoquinones of *Dionaea muscipula* from *in vitro* cultures. Phytochemistry. 1996;41:775-8. DOI: 10.1016/0031-9422(96)89675-0.
53. Tokunaga T, Takada N, Ueda M. Mechanism of antifeedant activity of plumbagin, a compound concerning the chemical defense in carnivorous plant. Tetrahedron Lett. 2004;45:7115-9. DOI: 10.1016/j.tetlet.2004.07.094.
54. Hsieh YJ, Lin LC, Tsai TH. Determination and identification of plumbagin from the roots of *Plumbago zeylanica* L. by liquid chromatography with tandem mass spectrometry. J Chromatogr A. 2005;1083:141-5. DOI: 10.1016/j.chroma.2005.06.030.
55. Binder RG, Benson ME, Flath RA. Eight 1, 4-naphthoquinones from Juglans. Phytochemistry. 1989;28: 2799-801. DOI: 10.1016/S0031-9422(00)98092-0.
56. Hedin PA, Collum DH, Langhans VE, Graves CH. Distribution of juglone and related compounds in pecan and their effect on *Fusicladium effusum*. J Agric Food Chem. 1980;28:340-2. DOI: 10.1021/jf60228a026.
57. Raj G, Kurup R, Hussain AA, Baby S. Distribution of naphthoquinones, plumbagin, droserone, and 5-O-methyl droserone in chitin-induced and uninduced Nepenthes khasiana: molecular events in prey capture. J Exp Bot. 2011;62:5429-36. DOI: 10.1093/jxb/err219.
58. Aung HH, Chia LS, Goh NK, Chia TF, Ahmed AA, Pare PW, *et al*. Phenolic constituents from the leaves of the carnivorous plant Nepenthes gracilis. Fitoterapia. 2002;73:445-7. DOI: 10.1016/S0367-326X(02)00113-2.
59. Kawiak A, Piosik J, Stasilojc G, Wisniewska GA, Marczak L, Stobiecki M, *et al*. Induction of apoptosis by plumbagin through reactive oxygen species-mediated inhibition of topoisomerase II. Toxicol Appl Pharmacol. 2007;223:267-76. DOI: 10.1016/j.taap.2007.05.018.
60. Acharya BR, Bhattacharyya B, Chakrabarti G. The natural naphthoquinone plumbagin exhibits antiproliferative activity and disrupts the microtubule network through tubulin binding. Biochemistry. 2008;47:7838-45. DOI: 10.1021/bi800730q.
61. Sandur SK, Ichikawa H, Sethi G, Ahn KS, Aggarwal BB. Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) suppresses NF-kappaB activation and NF-kappaB-regulated gene products through modulation of p65 and IkappaBalpha kinase activation, leading to potentiation of apoptosis induced by cytokine and chemotherapeutic agents. J Biol Chem. 2006;281:17023-33. DOI: 10.1074/jbc.M600135200.
62. Li L, Huang J, Xu X, Zhang Y, Cheng K, Yu P. Study on chemical constituents of *Drosera peltata* var. multisepala. Zhongguo Zhong Yao Za Zhi. 2012;37:222-5.
63. Gu JQ, Graf TN, Lee D, Chai HB, Mi Q, Kardono LB, *et al*. Cytotoxic and antimicrobial constituents of the bark of Diospyros maritima collected in two geographical locations in Indonesia. J Nat Prod. 2004;67:1156-61. DOI: 10.1021/np040027m.
64. Lin LC, Yang LL, Chou CJ. Cytotoxic naphthoquinones and plumbagic acid glucosides from *Plumbago zeylanica*. Phytochemistry. 2003;62:619-22. DOI: 10.1016/S0031-9422(02)00519-8.
65. Whitson EL, Sun H, Thomas CL, Henrich CJ, Sayers TJ, McMahon JB, *et al*. Synergistic trail sensitizers from Barleria alluaudii and Diospyros maritima. J Nat Prod. 2012;75:394-9. DOI: 10.1021/np200805z.
66. Budzianowski J, Budzianowska A, Kromer K. Naphthalene glucoside and other phenolics from the shoot and callus cultures of *Drosophyllum lusitanicum*. Phytochemistry. 2002;61:421-5. DOI: 10.1016/S0031-9422(02)00258-3.
67. Bringmann G, Rischer H, Wohlfarth M, Schlauer J, Assi LA. Droserone from cell cultures of *Triphyophyllum peltatum* (Dioncophyllaceae) and its biosynthetic origin. Phytochemistry. 2000;53:339-43. DOI: 10.1016/S0031-9422(99)00543-9.
68. Sidhu G, Sankaram A. A new biplumbagin and 3-chloroplumbagin from *Plumbago zeylanica*. Tetrahedron Lett. 1971;12:2385-8. DOI: 10.1016/S0040-4039(01)96870-4.
69. Sultana N, Akhter M, Khatoon Z. Nematicidal natural products from the aerial parts of Rubus niveus. Nat Prod Res. 2010;24:407-15. DOI: 10.1080/14786410802696429.
70. Verma S, Singh A, Mishra A. Gallic acid: Molecular rival of cancer. Environ Toxicol Pharmacol. 2013;35:473-85. DOI: 10.1016/j.etap.2013.02.011.
71. Weidner S, Rybarczyk A, Karamac M, Krol A, Mostek A, Grebosz J, *et al*. Differences in the phenolic composition and antioxidant properties between *Vitis coignetiae* and *Vitis vinifera* seeds extracts. Molecules. 2013;18:3410-26. DOI:10.3390/molecules18033410
72. Chandramohan Reddy T, Bharat Reddy D, Aparna A, Arunasree KM, Gupta G, Achari C, *et al*. Anti-leukemic effects of gallic acid on human leukemia K562 cells: downregulation of COX-2, inhibition of BCR/ABL kinase and NF-kappaB inactivation. Toxicol *in vitro*. 2012;26:396-405. DOI:10.1016/j.tiv.2011.12.018
73. González LAJ, Truchado P, Barberán TFA, Lázaro LM, Barradas MCD, Martín-Cordero C. Phenolic acids, flavonols and anthocyanins in *Corema album* (L.) D. Don berries. J Food Compost Anal. 2013;29:58-63. DOI:10.1016/j.jfca.2012.10.003
74. Ao C, Li A, Elzaawely AA, Xuan TD, Tawata S. Evaluation of antioxidant and antibacterial activities of *Ficus microcarpa* L. fil extract. Food Control. 2008;19:940-8. DOI:10.1016/j.foodcont.2007.09.007
75. Cottle W, Kolattukudy PE. Biosynthesis, deposition, and partial characterization of potato suberin phenolics. Plant Physiol. 1982;69:393-9. DOI:10.1104/pp.69.2.393
76. Lirdprapamongkol K, Sakurai H, Kawasaki N, Choo MK, Saitoh Y, Aozuka Y, *et al*. Vanillin suppresses *in vitro* invasion and *in vivo* metastasis of mouse breast cancer cells. Eur J Pharm Sci. 2005;25:57-65. DOI:10.1016/j.ejps.2005.01.015

77. Shahidi F, Perera N. Oil and phytochemicals from small fruit seeds. In: Ho CT, Shahidi F, Contis ET, editors. Nutrition, Functional and Sensory Properties of Foods. Cambridge: RSC Publishing; c2013. p. 224-30.
78. Hudson EA, Dinh PA, Kokubun T, Simmonds MS, Gescher A. Characterization of potentially chemo preventive phenols in extracts of brown rice that inhibit the growth of human breast and colon cancer cells. Cancer Epidemiol Biomarkers Prev. 2000;9:1163-70.
79. Chen FF, Wang GY, Shi YP. Molecularly imprinted polymer microspheres for solid-phase extraction of protocatechuic acid in *Rhizoma homalomenae*. J Sep Sci. 2011;34:2602-10. DOI:10.1002/jssc.201100463
80. Lin HH, Chen JH, Wang CJ. Chemopreventive properties and molecular mechanisms of the bioactive compounds in *Hibiscus sabdariffa* Linne. Curr Med Chem. 2011;18:1245-54. DOI:10.2174/092986711795029663
81. Qing ZJ, Yong W, Hui LY, Yong LW, Long LH, Ao DJ, *et al*. Two new natural products from the fruits of Alpinia oxyphylla with inhibitory effects on nitric oxide production in lipopolysaccharide-activated RAW264.7 macrophage cells. Arch Pharm Res. 2012;35:2143-6. DOI:10.1007/s12272-012-1211-7
82. Tang RN, Qu XB, Guan SH, Xu PP, Shi YY, Guo DA. Chemical constituents of *Spatholobus suberectus*. Chin J Nat Med. 2012;10:32-5. DOI: 10.3724/SP.J.1009.2012.00032
83. Lin HH, Chen JH, Chou FP, Wang CJ. Protocatechuic acid inhibits cancer cell metastasis involving the down-regulation of Ras/Akt/NF-kappaB pathway and MMP-2 production by targeting RhoB activation. Br J Pharmacol. 2011;162:237-54. DOI:10.1111/j.1476-5381.2010.01022.x
84. Rajendra Prasad N, Karthikeyan A, Karthikeyan S, Reddy BV. Inhibitory effect of caffeic acid on cancer cell proliferation by oxidative mechanism in human HT-1080 fibrosarcoma cell line. Mol Cell Biochem. 2011;349:11-9. DOI:10.1007/s11010-010-0655-7
85. Jaganathan SK. Growth inhibition by caffeic acid, one of the phenolic constituents of honey, in HCT 15 colon cancer cells. Scientific World Journal. 2012;2012:372345. DOI: 10.1100/2012/372345
86. Gomathinayagam R, Sowmyalakshmi S, Mardhatillah F, Kumar R, Akbarsha MA, Damodaran C. Anticancer mechanism of Plumbagin, a natural compound, on non-small cell lung cancer cells. Anticancer Res. 2008;28:785-92.
87. Sinha S, Pal K, Elkhanany A, Dutta S, Cao Y, Mondal G, *et al*. Plumbagin inhibits tumorigenesis and angiogenesis of ovarian cancer cells *in vivo*. Int J Cancer. 2013;132:1201-12. DOI:10.1002/ijc.27724
88. Thasni KA, Ratheeshkumar T, Rojini G, Sivakumar KC, Nair RS, Srinivas G, *et al*. Structure activity relationship of plumbagin in BRCA1 related cancer cells. Mol Carcinog. 2013;52:392-403. DOI: 10.1002/mc.21877
89. Strand LP, Scheline RR. The metabolism of vanillin and isovanillin in the rat. Xenobiotica. 1975;5:49-63. DOI:10.3109/00498257509056093
90. Tanaka T, Tanaka T, Tanaka M. Potential cancer chemo preventive activity of protocatechuic acid. J Exp Clin Med. 2011;3:27-33.
91. Baskaran N, Manoharan S, Balakrishnan S, Pugalendhi P. Chemo preventive potential of ferulic acid in 7,12-dimethylbenz[a]anthracene-induced mammary carcinogenesis in sprague-dawley rats. Eur J Pharmacol. 2010;637:22-9. DOI: 10.1016/j.ejphar.2010.03.054