

Pharmacological Activity of Vinca Alkaloids

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Research Article

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ABSTRACT

Vinca alkaloids are a set of drugs obtained from the periwinkle plant. They are naturally extracted from the plant *Catharanthus roseus*, and have hypoglycemic and cytotoxic effects. These are used to treat diabetes, high blood pressure and are also used as disinfectants. The vinca alkaloids are important as they can fight against cancer. The four major vinca alkaloids having medicinal properties are: Vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS). Vinflunine is a new synthetic vinca alkaloid, which has been approved in Europe for the treatment of second-line transitional cell carcinoma of the urothelium. Vinca alkaloids are the second-most-used class of cancer drugs.

INTRODUCTION

Catharanthus roseus is generally known as Madagascar periwinkle and belongs to the family Apocynaceae. It is cultivated for its herbal use and as ornamental plant (**Figure 1**). Alkaloids are set of organic compounds made up of carbon, hydrogen, nitrogen and oxygen and are derived from plant. Vinca alkaloids are the oldest group of the plant alkaloid groups that used to treat cancer [1-7].



Figure 1. *Catharanthus roseus* plant.

Vinca alkaloids were discovered in the 1950's by Robert Noble and Charles Beer of Canada. Medicinal uses of this plant led to the monitoring of its compounds for their hypoglycemic activity and cytotoxic effect. These are used to treat diabetes, high blood pressure and also used as disinfectants. However, vinca alkaloids are of main importance due to their cancer fighting ability [8-14]. The four major vinca alkaloids having medicinal use are: Vinblastine, vinorelbine, vincristine and vindesine, but only Vinblastine, vinorelbine, vincristine are approved for use in the United States. There also exists a novel vinca alkaloid, vinflunine that is currently approved in Europe for medicinal treatment [15-19].

MECHANISM OF ACTION

The vinca alkaloid cytotoxicity is due to the synergy with tubulin and disruption of microtubule function. This occurs mainly in the microtubules comprising the mitotic spindles, causing the arrest of metaphase (**Figure 2A and 2B**) [20-26]. There are many other biochemical activities of these alkaloids that may or may not be related to their effect on microtubules. After the treatment of the cells with doses of vinca alkaloids, there doesn't show any effect on the microtubules. Vinca alkaloids and other antimicrotubule agents have effect on non-malignant as well as malignant cells in the non-mitotic cell division, because microtubules are involved in many non-mitotic functions.

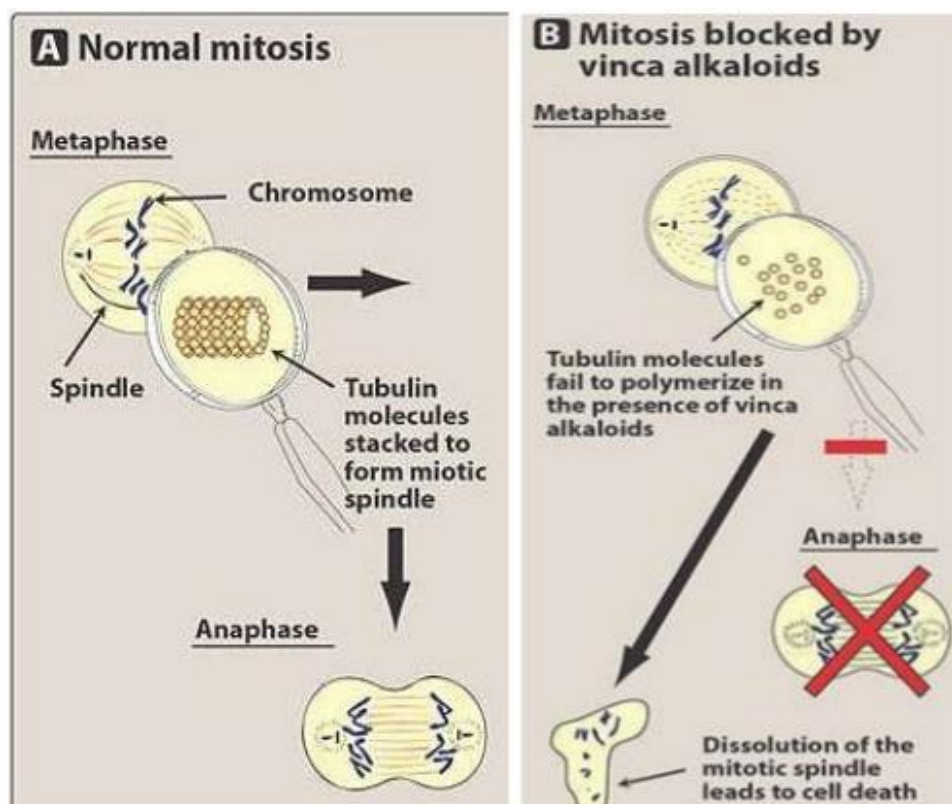


Figure 2. A) Normal mitosis; B) Mitosis blocked by vinca alkaloids.

Vinca alkaloids bind to the receptor sites on tubulin and separate from the taxanes, colchicine, podophylotoxin and guanosine-5'-triphosphate. Binding occurs rapidly as well as slowly. There exist two vinca alkaloid binding sites per mole of tubulin dimer. There are 16-17 high-affinity binding sites that are located at the end of the microtubule. Binding of the vinca alkaloids to the binding site of tubulin interrupts microtubule segregation, but one of the most important effects of low drug concentration of vinca alkaloid is decrease growth rate and shortening at the assembly end of the microtubule, which cause a "kinetic cap" and suppresses function (**Figure 3**) [26-33].

Vinca alkaloids inhibit malignant angiogenesis *in vitro*. For example, Vinblastine with concentrations of 0.1 to 1.0 pmol/L blocks endothelial proliferation, chemotaxis and spreading on fibronectin but other fibroblasts and lymphoid tumors remain unaffected at these low concentrations [34-42]. Low doses of Vinblastine in combination with antibodies against vascular endothelial growth factor increase antitumor response even in tumors resistant to direct cytotoxic effects of drug. Vincristine and related compounds produce destabilization of microtubules by binding to tubulin and blocking the polymerization.

MEDICINAL USES AND TOXICITY

Vinca alkaloids are generally used in combination chemotherapy regimens for medicinal therapies. They do not have cross-resistance with drugs that alkylate DNA and whose mechanism of action is different. Vinblastine is

used in medicinal treatment for testicular carcinoma, Hodgkin Lymphoma and Non-Hodgkin lymphoma. It is also used in curing of breast cancer and germ cell tumors. Side-effects of Vinblastine include nausea, vomiting, constipation, toxicity to white blood cells, dyspnea, chest pain, wheezing and fever. It is rarely associated in the secretion of antidiuretic hormone [43-48].

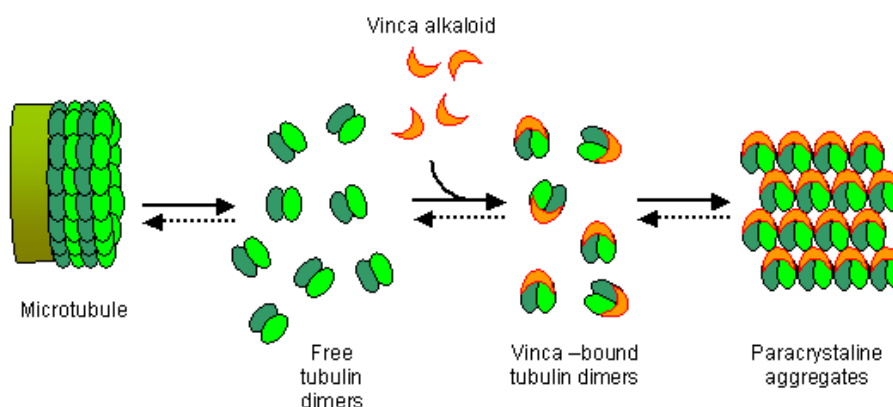


Figure 3. Binding of vinca alkaloids on receptor sites on tubulin.

Vinorelbine is similar to Vinblastine. It has antitumor activity against breast cancer and can be effective against bone tumor cells, osteosarcoma. In addition, Vinorelbine decreases the stability of lipid bilayer membranes. Side-effects of Vinorelbine include decreased resistance to infection, bleeding, anemia, constipation, diarrhea, nausea, numbness or tingling in the hands and feet, fatigue and inflammation at the injection site [49-53].

Vincristine is used to treat acute leukemia, rhabdomyosarcoma, neuroblastoma, Wilm's tumor, Hodgkin's disease and other lymphomas. Vincristine is also used for treating several non-malignant hematologic disorders. The most common side-effects of Vincristine are peripheral neuropathy, bone marrow activity suppression, constipation, toxicity of nervous system, nausea and vomiting [54-67].

Vindesine is similar to Vinblastine in pharmacological activity. Vindesine also possess Antineoplastic activity and is seen in acute lymphocytic leukemia, chronic myeloid leukemia, malignant melanoma, pediatric solid tumors and metastatic renal, breast, esophageal and colorectal carcinomas [68-74]. A new synthetic vinca alkaloid was developed through the addition of two fluorine molecules by super acidic chemistry and is named as Vinflunine (Figure 4). Vinflunine is the first fluorinated inhibitor of microtubule that belongs to vinca alkaloids. Vinflunine is used in Europe for the treatment of second-line transitional cell carcinoma of the urothelium (TCCU) [75-83].

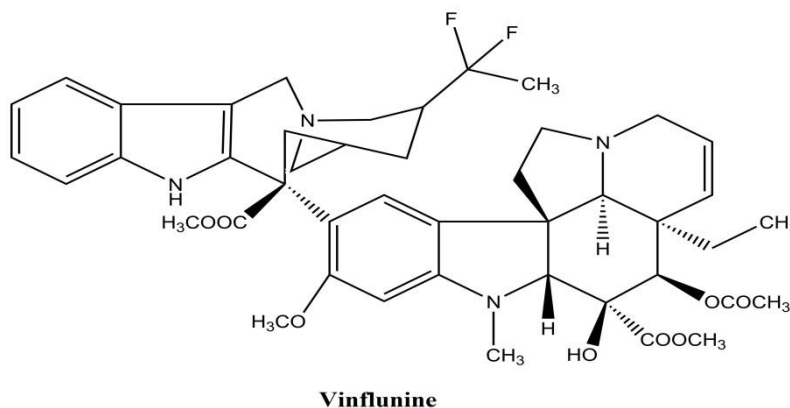


Figure 4. Structural formula of Vinflunine.

Vinca alkaloids are quite similar in structure (Figure 5) but their toxicologic profiles are extensively different. All vinca alkaloids produce peripheral neurotoxicity, but Vincristine is more potent compared to other vinca alkaloids [84-89]. The primary pathological effect of vinca alkaloids is axonal degeneration. The uptake of Vincristine into the brain is low and there also observed infrequent central nervous system effects, such as confusion, mental status changes, depression, hallucinations and visual disturbances. Laryngeal paralysis was also reported at times. The only effective way to reduce neurotoxicity caused by vinca alkaloid is by discontinuing treatment or by decreasing the dose and dosing frequency. Neutropenia is the main dose-limiting toxicity of Vinblastine, Vindesine and Vinorelbine. Thrombocytopenia and anemia rarely reported. Vincristine rarely causes hematologic toxicity; severe myelosuppression has been monitored in situations resulting in profoundly increased drug exposure and hepatic deficiency [90-94].

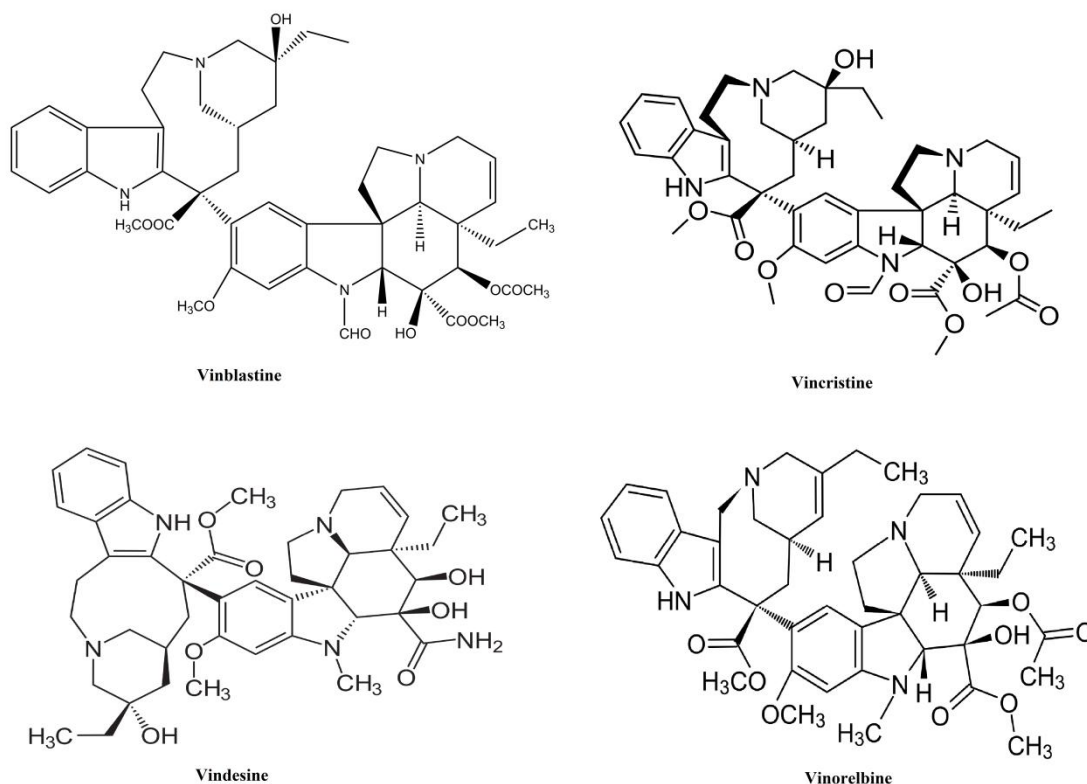


Figure 5. Structural formula of major Vinca alkaloids: Vinblastine, Vincristine, Vindesine, Vinorelbine.

Gastrointestinal toxicities may be observed with the usage of vinca alkaloids. Vincristine or high doses of the other vinca alkaloids cause gastrointestinal autonomic dysfunction which includes constipation, ileus and abdominal pain. Mucositis occurs more frequently with Vinblastine than Vinorelbine and is common with Vincristine. Nausea, vomiting and diarrhea were also reported.

The vinca alkaloids are effective vesicants and these may lead to tissue damage also. Acute cardiac ischemia, chest pains without ischemia, fever without an obvious source, acute pulmonary effects, Raynaud phenomenon have also been reported with the use of vinca alkaloids [95-97].

Vinca alkaloids are contraindicated during pregnancy, have been planning for pregnancy or during breast-feeding as it may cause birth abnormalities. Patients should not receive any vaccinations while taking this medication. Vincristine may also cause weakness of immunity system and can lead to an illness. Patients should notify their clinician in prior about any prescription drugs taken concurrently and also suffering with any other medical conditions, such as, herpes zoster infection, gout, kidney stones, chickenpox, infections, liver disease, nerve or muscle disease [98-100]. However, the drug concentration and treatment duration are of main importance for determining drug accumulation and cytotoxicity.

CONCLUSION

Vinca alkaloids are generally used in Chemotherapy of Cancer. They do not have cross-resistance with drugs that alkylate DNA. They are used to treat diabetes, high blood pressure, etc. These are also used as disinfectants. Vinca alkaloids have cytotoxic effect that arrests the cell division and finally causes death of the cells. The four major vinca alkaloids used clinically are Vinblastine, Vinorelbine, Vincristine and Vindesine. Vinflunine is a synthetic vinca alkaloid which has been in use recently for the treatment of second-line transitional cell carcinoma of the urothelium and other malignancies. Overall, vinca alkaloids are the second most-used class of cancer drugs. Different researches and studies for new vinca alkaloid applications are being carried out in this regard.

REFERENCES

1. Guest TC and Rashid S. Anticancer Laccases: A Review. *J Clin Exp Oncol.* 2016;5:153.
2. Lydia J and Sudarsanam D. Anticarcinogenic Effects of Selected Alkaloids Identified from *Cyperus Rotundus*: An In Silico Perspective. *J Appl Bioinform Comput Biol.* 2016;5:122.
3. Panchangam RBS and Dutta T. Engineered Nanoparticles for the Delivery of Anticancer Therapeutics. *J Pharm Drug Deliv Res.* 2015;4:127.
4. Swasthi K and Sinha P. Nickel Stress Induced Antioxidant Defence System in Sponge Gourd (*Luffa Cylindrical*). *J Plant Physiol Pathol.* 2013;1:102.
5. Chiririwa H. Synthesis, Characterization of Gold (III) Complexes and an in vitro Evaluation of their Cytotoxic Properties. *J Pharm Sci Emerg Drugs.* 2014;2:104.
6. Lawania RD and Mishra A. Anticancer Potential of Plants and Natural Products: A Review. *J Pharmacol Biomed Anal.* 2013;1:103.
7. Shetty AA, et al. Vegetables as Sources of Antioxidants. *J Food Nutr Disor.* 2013;2:104.
8. Rani A. Medicinal Significance of *Aegle marmelos* (Bael). *Vegetos.* 2012;25:320-323.
9. Kumar A and Sarin NB. RNAi: A Promising Approach to Develop Transgenic Plants Against Geminiviruses and Insects. *J Plant Physiol Pathol.* 2013;1:103.
10. Yadav MS. Response of ashwagandha [*Withania somnifera* (L.) Dunal] to integrated nutrient management system (INMS). *Crop Res.* 2013;45:276-279.
11. Zimowska B. Occurrence and Characterization of *Phyllosticta plantaginis*. *J Plant Physiol Pathol.* 2013;1:101.
12. Bakakina YS, et al. Low and High Temperatures Enhance Guanylyl Cyclase Activity in *Arabidopsis* Seedlings. *J Plant Physiol Pathol.* 2014;2:132.
13. Ren YL, et al. Analysis of Embryo, Cytoplasmic and Maternal Effects on Seven Essential Amino Acid Traits in Rapeseed. *J Plant Physiol Pathol.* 2014;2:133.
14. Mahmoud AFA and Abo-Elyousr KAM. Genetic Diversity and Biological Control of *Rhizoctonia solani* Associated with Root Rot of Soybean in Assiut Governorate, Egypt. *J Plant Physiol Pathol.* 2014;2:134.
15. Tanabe S, et al. Spatial Regulation of Defense-Related Genes Revealed by Expression Analysis using Dissected Tissues of Rice Leaves Inoculated with *Magnaporthe oryzae*. *J Plant Physiol Pathol.* 2014;2:135.
16. Schlosser AJ, et al. Enhanced Rice Growth is Conferred by Increased Leaf ADP-Glucose Pyrophosphorylase Activity. *J Plant Physiol Pathol.* 2014;2:136.
17. Jahan AA and Anis M. Changes in Antioxidative Enzymatic Responses during Acclimatization of In Vitro Raised Plantlets of *Cardiospermum halicacabum* L. against Oxidative Stress. *J Plant Physiol Pathol.* 2014;2:137.
18. Cruz AF, et al. Impact of the Arbuscular Mycorrhizal Fungi and Bacteria on Biocontrol of White Root Rot in Fruit Seedlings. *J Plant Physiol Pathol.* 2014;2:114.
19. Cruz AF, et al. Soil-Borne Plant Pathogens Associated to Decline of Grapevine Grown in Greenhouse. *J Plant Physiol Pathol.* 2014;2:115.
20. Singh AU and Prasad D. Management of Plant-parasitic Nematodes by the Use of Botanicals. *J Plant Physiol Pathol.* 2014;2:116.
21. Seleim MA, et al. Peroxidase and Polyphenoloxidase Activities as Biochemical Markers for Biocontrol Efficacy in the Control of Tomato Bacterial Wilt. *J Plant Physiol Pathol.* 2014;2:117.
22. Thivya N, et al. Phytoaccumulation of Chromium and Copper by *Mentha spicata* L. *J Plant Physiol Pathol.* 2014;2:118.

23. Sinha P. Modulation of Oxidative Stress Responsive Enzymes and Non-Enzymatic Components by Excess Nickel in *C. Lanatus Lanatus* Var. *Fistulosus*. *J Plant Physiol Pathol*. 2014;2:119.
24. Mohapatra S and Mittra B. Induction of Glutathione, Ascorbate and Associated Enzymes by a Low Dose CdCl₂ Pre-treatment Alleviate Fusarium Induced Oxidative Stress in Wheat. *J Plant Physiol Pathol*. 2016;4:141.
25. Gupta DK, et al. Moderate Uranium Disturbs the Nutritional Status and Induces Oxidative Stress in *Pisum sativum* L. *J Plant Physiol Pathol*. 2016;4:142.
26. Abduyeva-Ismayilova SM. Effect of Physiological Acid Salts on Swelling, Germination and Growth Processes of Seedlings. *J Plant Physiol Pathol*. 2016;4:143.
27. Bezić N, et al. *Helichrysum italicum* (Roth) G. Don - Essential Oil Composition and Activity on Tobacco Mosaic Virus Infection. *J Plant Physiol Pathol*. 2016;4:144.
28. Nomura H and Shiina T. Plant Endosymbiotic Organellar Calcium Signaling under Biotic and Abiotic Stresses. *J Plant Physiol Pathol*. 2016;4:145.
29. Vaidya S, et al. Impact of Elevated CO₂ on Growth and Physiological Parameters of Groundnut (*Arachis hypogaea* L.) Genotypes. *J Plant Physiol Pathol*. 2015;3:138.
30. Dewir YH, et al. Antioxidative Capacity and Electrolyte Leakage in Healthy Versus Phytoplasma Infected Tissues of *Euphorbia coerulescens* and *Orbea gigantea*. *J Plant Physiol Pathol*. 2015;3:139.
31. Pillai G and Jayaraj R. Identification of Endophytic Fungi/opportunistic Pathogen from the Perennial Herb of *Amaranthaceae* Family. *J Plant Physiol Pathol*. 2015;3:140.
32. Dang QL. Improving the Quality and Reliability of Gas Exchange Measurements. *J Plant Physiol Pathol*. 2013;1:e101.
33. Creamer R and Baucom D. Fungal Endophytes of Locoweeds: A Commensal Relationship? *J Plant Physiol Pathol*. 2013;1:104.
34. Leo Daniel AE, et al. Effect of Polymeric Additives, Adjuvants, Surfactants on Survival, Stability and Plant Growth Promoting Ability of Liquid Bioinoculants. *J Plant Physiol Pathol*; 2013;1:105.
35. Shi CH, et al. Analysis of Genetic Relationships between Seed Nutrient Traits and Plant Agronomic Traits in *Indica* Rice (*Oryza sativa* L.). *J Plant Physiol Pathol*; 2013;1:106.
36. Srivastava S and Sharma YK. Arsenic Phytotoxicity in Black Gram (*Vigna Mungo* L. Var. PU19) and its Possible Amelioration by Phosphate Application. *J Plant Physiol Pathol*. 2013;1:107.
37. Freire MGM, et al. Effect of Castor Bean Oil on Post-harvest Fungal Pathogen of Coconut: *Lasiodiplodia theobromae*. *J Plant Physiol Pathol*. 2013;1:108.
38. Malafaia CB, et al. Evaluation of the Resistance and Differential Induction of Chitinases in Tomato in Response to Inoculation with *Fusarium oxysporum* f. sp. *lycopersici*. *J Plant Physiol Pathol*. 2013;1:109.
39. Kumar V, et al. Initial Population Density its Effect on the Pathogenic Potential and Population Growth of *Rotylenchulus reniformis* on Cowpea (*Vigna unguiculata* L.). *J Plant Physiol Pathol*. 2013;1:110.
40. Reggia L, et al. *Arabidopsis* Rapid Movement Response to Electrical Stimulation. *J Plant Physiol Pathol*. 2016;4:146.
41. Kumar S, et al. Heterosis and Inbreeding Depression in Tropical Sweet Sorghum (*Sorghum bicolor* (L.) Moench). *J Plant Physiol Pathol*. 2016;4:147.
42. Mishra P and Prasad SM. Mounting Insights over Human Wellness by Utilizing Plant's Primed Defense against Precise/Mild Oxidative Stress. *J Plant Physiol Pathol*. 2016;4:148.
43. Sipai AH, et al. Effect of Phosphorus, Sulphur and Biofertilizer on Growth, Yield and Nodulation in Mungbean on Loamy Sand Soils of Kutch. *J Plant Physiol Pathol*. 2016;4:149.
44. Yinyan S, et al. Development and Prototype Experiment of Environmental Self-Propelled and Orderly Harvester for *Artemisia selengensis* Turcz. *J Plant Physiol Pathol*. 2016;4:150.
45. Oliveira JTA, et al. Role of Antioxidant Enzymes, Hydrogen Peroxide and PR-Proteins in the Compatible and Incompatible Interactions of Cowpea (*Vigna unguiculata*) Genotypes with the Fungus *Colletotrichum gloeosporioides*. *J Plant Physiol Pathol*. 2014;2:131.
46. Sobhy II AH, et al. Effect of Certain Plant Extracts to Control Purple Blotch Disease of Onion Plants (*Allium cepa* L.). *Upas*. *J Plant Physiol Pathol*. 2013;1:111.
47. Sinha P, et al. Oxidative Stress Responsive Enzymes and Non-Enzymatic Components in Response to Excess Cadmium in Pigeon Pea (*Cajanus cajan* Mill) Cv. *Upas*. *J Plant Physiol Pathol*. 2013;1:112.
48. Srivastava S and Sharma YK. Altered Growth, Photosynthetic Machinery and Induced Oxidative Stress in Spinach in Response to Arsenic Stress. *J Plant Physiol Pathol*. 2013;1:113.

49. Ye Z and Dyke KV. Antimalarial Activity of Various Bisbenzylisoquinoline and Aporphine-Benzylisoquinoline Alkaloids and their Structure-Activity Relationships against Chloroquine – Sensitive and Resistant Plasmodium falciparum Malaria in vitro. *Malaria Contr Elimination*. 2015;4:137.
50. Gopal R and Sharma YK. Effects of Chromium (VI) on Groundnut (*Arachis Hypogaeae* L.) Metabolism. *J Plant Physiol Pathol*. 2014;2:120.
51. Amri E. Variation in Pre-Dispersal Seed Predation and Seed Traits among Provenances of *Dalbergia Melanoxylon* (Guill. & Perr.). *J Plant Physiol Pathol*. 2014;2:121.
52. Abo-Elyousr KAM, et al. Enhance Suppressive Effect of Compost on Soybean Rhizoctonia Root Rot by Soil Treatment with *Trichoderma harzianum*. *J Plant Physiol Pathol*. 2014;2:122.
53. Rosmana A, et al. Low Water Availability Enhancing Soil Receptivity to Fusarium Pathogen: Case of Root Rot on Mulberry. *J Plant Physiol Pathol*. 2014;2:123.
54. Dutta P, et al. Interactive Effect of Arsenic Stress and Seed Phytate Content on Germination and Seedling Development of Different Vegetable Crops. *J Plant Physiol Pathol*. 2014;2:124.
55. Ajay Kumar G. *Colletotrichum gloeosporioides*: Biology, Pathogenicity and Management in India. *J Plant Physiol Pathol*. 2014;2:125.
56. Kapadia N and Harding W. Aporphine Alkaloids as Ligands for Serotonin Receptors. *Med Chem (Los Angeles)*. 2016;6:241-249.
57. Wau J, et al. Isolation of Three Bioactive Phenantroindolizidine Alkaloids from the Fruit Latex of *Ficus botryocarpa* Miq. *Nat Prod Chem Res*. 2015;3:197.
58. Khan H. Therapeutic Potential of Alkaloids Cough. *Biol Med (Aligarh)*. 2016;8:e123.
59. Mayevych I, et al. Chemical Composition of *Cordia lutea* L.: Absence of Pyrrolizidine Alkaloids. *Nat Prod Chem Res*. 2015;3:194.
60. Camacho E, et al. Regulation of the Human Delta-Opioid Receptor by Alkaloids: Different Roles of Arrestins. *Neurochem Neuropharm Open Access*. 2015;1:101.
61. Wang D, et al. Activities of Antitussive of even Alkaloids from *Bulbus Fritillariae cirrhosae*. *Nat Prod Chem Res*. 2014;S1:005.
62. Ortega-David E and Rodriguez-Stouvenel A. Bioprocessing of Lupin Cotyledons (*Lupinus mutabilis*) with *Rhizopus oligosporus* for Reduction of Quinolizidine Alkaloids. *J Food Process Technol*. 2014;5:323.
63. Putra MY and Jaswir I. The Alkaloids from Indonesian Marine Sponges. *Oceanography*. 2014;2:125.
64. Schaafsma E, et al. Anticancer Activities of Resveratrol in Colorectal Cancer. *Biol Med (Aligarh)*. 2016;8:317.
65. Agrawal P. Non-Coding Ribonucleic Acid: A New Anticancer Drug Target. *J Pharmacovigil*. 2016;4:e158.
66. Shabani A. A review of Anticancer Properties of Herbal Medicines. *J Pharma Care Health Sys*. 2016;3:160.
67. Fawzy A, et al. Kinetics and Mechanistic Approach to Palladium (II)-Catalyzed Oxidative Deamination and Decarboxylation of Leucine and Isoleucine by Anticancer Platinum (IV) Complex in Perchlorate Solutions. *Mod Chem Appl*. 2016;4:182.
68. Soave C, et al. Repositioning an Old Anti-Alcoholism Drug: Disulfiram as a Selective, Effective and Economical Anticancer Agent. *J Develop Drugs*. 2016;5:e147.
69. Shaimaa GA, et al. Phytochemical Screening, Antioxidant Activities and In Vitro Anticancer Potential of Egyptian *Capsicum* Spp. *Biochem Pharmacol (Los Angel)*. 2016;5:205.
70. Rosa LS, et al. Anticancer Properties of Phenolic Acids in Colon Cancer – A Review. *J Nutr Food Sci*. 2016;6:468.
71. Siqueira EP, et al. *Chamae Costus subsessilis* and *Chamae Costus cuspidatus* (Nees & Mart) C. Specht and D.W. Stev as Potential Sources of Anticancer Agents. *Nat Prod Chem Res*. 2016;4:204.
72. Punganuru SR, et al. Colchicine-Based Hybrid Anticancer Drugs to Combat Tumor Heterogeneity. *Med Chem (Los Angeles)*. 2016;6:165-173.
73. Mastrangelo D, et al. The Cure from Nature: The Extraordinary Anticancer Properties of Ascorbate (Vitamin C). *J Integr Oncol*. 2016;5:157.
74. Emmanuel A, et al. Preliminary Identification of Lactate Dehydrogenase Inhibitors towards Anticancer Drug Development. *J Develop Drugs*. 2015;4:132.
75. Al-Khodir FAI. Synthesis, Spectroscopic and Biologically Assessments of Calcium(II), Zinc(II), Palladium(II) and Gold(III) Sulfacetamide Sodium Complexes: Gold(III) Nano Medical Complex as an Anticancer Agent. *J Nanomed Nanotechnol*. 2015;6:326.
76. Lu DY, et al. Anticancer Drug Combinations, A Big Momentum is Needed. *Metabolomics*. 2015;5:e139.

77. Noro J, et al. Evaluation of New Naphthalimides as Potential Anticancer Agents against Breast Cancer MCF-7, Pancreatic Cancer BxPC-3 and Colon Cancer HCT-15 Cell Lines. *Organic Chem Curr Res*. 2015;4:144.
78. Huang C, et al. 3 β -Methoxy Derivation of Withaferin-a Attenuates its Anticancer Potency: Bioinformatics and Molecular Evidences. *Med Aromat Plants*. 2015;4:219.
79. Sun Y and Zhang B. Landscape and Targeting of the Angpt-Tie System in Current Anticancer Therapy. *Transl Med*. 2015;5:157.
80. Hani M and Eman H. Anticancer Compounds from *Chaetomium globosum*. *Biochem Anal Biochem*. 2015;4:174.
81. Zhu C and Cui L. The Role of Ahr in Anticancer Drug Resistance in Breast Cancer. *J Bioanal Biomed*. 2015;7:87-90.
82. Yurchenko EA, et al. Hsp70 Induction and Anticancer Activity of U-133, the Acetylated Trisglucosydic Derivative of Echinochrome. *Med Chem*. 2015;5:263-271.
83. Adcock AF, et al. Three- Dimensional (3D) Cell Cultures in Cell-based Assays for in-vitro Evaluation of Anticancer Drugs. *J Anal Bioanal Tech*. 2015;6: 247.
84. Halwani M, et al. Liposomal β -Glucan: Preparation, Characterization and Anticancer Activities. *J Nanomed Nanotechnol*. 2015;6:319.
85. Liu JJ, et al. Systems Pharmacology for the Study of Anticancer Drugs: Promises and Challenges. *Clin Pharmacol Biopharm*. 2015;4:140.
86. Saganuwan SA and Ndakotsu AM. Standardization and Scoring of the Body Surface Area (BSA) Formulas for Calculation of the Doses of Anticancer Agents for Cancer Patients from the North-Western Nigeria. *J Cancer Sci Ther*. 2015;7:012-018.
87. Abou-Ellella FM and Ali RFM. Antioxidant and Anticancer Activities of Different Constituents Extracted from Egyptian Prickly Pear Cactus (*Opuntia ficus-indica*) Peel. *Biochem Anal Biochem*. 2014;3:158.
88. Ananthula S. Bioavailability and Bioequivalence Issues Associated With Oral Anticancer Drugs and Effect on Drug Market. *J Bioequiv Availab*. 2014;6:e56.
89. Uddin MH, et al. Anticancer Strategy Targeting Mitochondrial Biogenesis in Ovarian Cancer. *J Cancer Sci Ther*. 2014;6:422-428.
90. Matsubara MM, et al. Depletion of RUVBL2 in Human Cells Confers Moderate Sensitivity to Anticancer Agents. *J Cancer Sci Ther*. 2014;6:440-445.
91. Venugopal DVR, et al. Synthesis, of Novel Piperine Analogs of Dipeptidyl Boronic Acid as Antimicrobial and Anticancer Agents. *Med Chem*. 2014;4:606-610.
92. Han DW. Advances of Green Tea Catechins towards Smart Anticancer Agents. *Biochem Pharmacol*. 2014;3:e153.
93. Abdelgawad MA, et al. Design, Synthesis and Anticancer Screening of Novel Pyrazole Derivatives Linking to Benzimidazole, Benzoxazole and Benzothiazole. *Med Chem*. 2014;S1:001.
94. Abd-Elsalam KA and Hashim AF. Hidden Fungi as Microbial and Nano- Factories for Anticancer Agents. *Fungal Genom Biol*. 2013;3:e115.
95. Ahsan MJ, et al. Synthesis, Anticancer and Molecular Docking Studies of 2-(4-chlorophenyl)-5- aryl-1,3,4-Oxadiazole Analogues. *Med Chem*. 2013;3:294-297.
96. Parkhill AL. Oral Mucositis and Stomatitis Associated with Conventional and Targeted Anticancer Therapy. *J Pharmacovigilance*. 2013;1:112.
97. McGuire K, et al. Vitamin C and K3 Combination Causes Enhanced Anticancer Activity against RT-4 Bladder Cancer Cells. *J Cancer Sci Ther*. 2013;5:325-333.
98. Shabana MM, et al. In Vitro and In Vivo Anticancer Activity of the Fruit Peels of *Solanum melongena* L. against Hepatocellular Carcinoma. *J Carcinogene Mutagene*. 2013;4:149.
99. Ngameni B, et al. Synthesis and Evaluation of Anticancer Activity of O-allylchalcone Derivatives. *Med Chem*. 2013;3:233-237.
100. Amin A and Lowe L. Plant-Based Anticancer Drug Development: Advancements and Hurdles. *J Gastroint Dig Syst*. 2012;2:e111.