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A case study – Regulation and functional mechanisms of cancer cells and control its activity using plants and their derivatives



Palaniselvam Kuppusamy, Mashitah M. Yusoff, Gaanty Pragas Maniam, Natanamurugaraj Govindan*

Mammalian Cell Technology Laboratory, Faculty of Industrial Sciences and Technology, Universiti Malaysia Pahang, Lebuhraya Tun Razak 26300, Gambang, Kuantan, Pahang, Malaysia

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ABSTRACT

Novel exploiting to the understanding of conventional medicine was followed by the findings of many unique secondary metabolites and its biological property and is highly required for treating of many endemic diseases. The plants have been a long background in ethno pharmacological knowledge for treatment of endemic and non-endemic diseases. Such plants are traditionally used in different form of paste, extraction and powder to treat seasonal diseases. Nowadays main uses of some medicinal plants have been a great deal with cure and control various chronic diseases such as cancer, AIDS, hepatitis, neurogenic disorders and acute kidney diseases. Cancer is molecular dysfunction and disarrangement in DNA base pairs it leads to change the human physiological and biochemical behavior of the system. Apoptotic mechanisms are regulating by two distinct pathways in which basic creeds perform in common to all eukaryotes. The key components in apoptosis especially mitochondrial intracellular organelles are identified (DNA, protein and ATP, Ca²⁺). These components control the next cellular binder step and participate in effecting cell suicide mechanisms. The diverse aspects of mitochondria involved in apoptosis include dealing with other proceedings such as release of protein or enzymes to effective for cell death. In these mechanism plants and related natural products using alternative therapeutic management, very less toxicity and cost benefits. Plant extracts and its biomass has revealed the existing of various pharmacologically active compounds like steroids, polyphenols, polysaccharides, saponins, alkaloids, tannins and terpenoids. The reliable natural products are acting as high sources for anticancer drugs. The natural derived compounds are the prolongation of life span of the zeolites and decrease of malignancy cell formation in the cellular system.

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* Corresponding author. Tel.: +60 142918824, +60 95492465 (office); fax: +60 95492766.

E-mail address: natanam80@gmail.com (N. Govindan).

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1. Introduction

The key challenging property and functional behavior of cancer cells having tremendous secret action in cellular and functional characteristics. The breaking surreptitious thing of shed by Reed Elegvier India Put. Ltd. All rights received the cancer related node is still not yet to be found. Still the scientific community are searching the mechanism of cell modification, biochemical-molecular pathway changes and genome expression. A sudden change of single or two more base pairs in a DNA will leads to form of solid tumor or malignant deposit. Observably the mechanism of tumor development requires advance molecular genomic studies and therapeutic drug molecules action is needed much more. Particularly in the malignant tumor are invasive, metastasis, mutagenic DNA modification, methylation and different genomic and proteomic expression. These are present in the major clinical challenges in which treatment of cancer.^{1,2} Even though the progress that understands of the mechanisms of carcinogen originating to modify the structural and functional property of DNA. The modern investigation of tumor by the identification of some biochemical substances, hormones and enzymes are involved signal transduction pathways. That compound may induce the cellular oncogenes and suppress/arrest the normal function.3,4 Over the past decade, there has been an increasing in the demand of drug development against cancer and related diseases. The plants have played a vital role in the treatment of chronic and acute diseases for the very long centuries ago. Nowadays natural products have been highly focused as an important tool for drug development and medicinal chemistry for production of less side effect drugs.^{5,6} The plant and its derivatives of chemical compound especially alkaloids, saponins polyphenols, terpenoids and tannins natural product studies suggest that reducing the cancer risk factor with low impact of side effects.^{7,8} Plants are mainly used as rapid progress in prevention and treatment of particularly for the cancers and related malignant diseases even though have not been particular site of action and mechanisms, where there is still strongly green chemistry drugs are needed for more active remedies.9 Conventional and modern methods are mainly plant and their products are considered to be one of the prospective sources for the anticancer agents with less adverse effect. Also other various sources of marine producers such as fungi, bacteria, seaweeds and algae are produces various bioactive compounds. That has been considered for their ability to treat and reduce the risk number of acute diseases and chronic diseases.¹⁰ Plant purified metabolites and its synthetic nanodrug molecules have been evaluated in clinical trials and marketed.^{11,12} On the basis, the present review focused on the potential of the anticancer effects of plant based compounds and its molecular behavior of malignant cell is also being compiled.

2. Metastatic behavior of cancer cell line

The tumor cell population or individual cell lines have differential accumulation of genetic changes and biochemical behavior contributes to the reported cases. Phenotype differences in malignant tumor cells have been well studied in morphology, development and gene expression of benign and malignant cells. Cancer cells have a multiple genetic alterations in the molecular dogma, especially the post-transcriptional mechanisms including frequent mutational changes in p53, caspase genes and miRNA transcriptional factors. Recently human breast cancer characterized its gene structure to study the metastatic behavior of cancer. The central part of MUC5B is composed of three alternating domains: i) the highly conserved domain is called CYS domain ii) a subdomain denoted is R domain, it fully made of repetitions and irregular repeat of 29 amino acid codons, it contains rich in Ser, Thr and Pro iii) a conserved sub domain has 111 amino acid it is called as R-end domain also repeated four in four times, the alternating CYS/R/R end domain build a large composite repeating unit of 528 amino acids.¹³ Other important findings to examine the main role that NK cells play in the regulation of metastatic spread of human tumour cells in host system. The development of tumour metastasis is regulated by a variety of tumour suppressor genes and/oncogene, including tumour suppress or gene nm23. The nm23 gene mainly characterized by its reduced expression of metastatic melanoma cell line compared with the other metastatic cell line. Hence nm23 gene contain eight number of gene family instead of nm23 - H1 is highly studied involving in cell proliferation differentiation and development. Recent literature were showed that the tumor cell behavior especially malignant cell secretes some messenger compounds in which attract neutrophil to activate protein kinase. It can degrade the extracellular matrix leading to tumor metastasis.14,15

3. In-vitro antiproliferation mechanisms

The plant combination (muthu marunthu) has been showed one of the common and notable features in poor growth rate of tumor cells. Also the muthu marunthu is combination plant biomass did not show any alteration of normal growing cells. The glycoproteins such as hexose, hexosamine, sialic acid and fucose are controlling the level in plasma by the treating of muthu marunthu (different plant extracts were formulated in various concentrations) fibrosarcoma rats. Hence muthu marunthu has very good controlling capacity on the biochemical events during tumor progression, without inducing any toxic effects for normal metabolism.¹⁶ The aqueous extract of Iresine herbstii was synthesized silver nanoparticles was performed by green synthesis and plant mediated nanoparticles showed potent cytotoxicity against HeLa cancer cells. Plant synthesized silver nanoparticles have induced over above 80% death of HeLa cell at a treatment of moderate concentration level is 300 mg/ml. The AgNPs are revealed a prominent activity of arrest metabolic function of fibroblast cells (IMR-90) at 400 mg concentration.

The Persea americana Nigerian traditional plant extracts were used for the treatment of anticancer studies. The plant extracts contains polar compounds that were responsible for suppress the division of cancer cells. Since it is well known that the phytochemicals have been shown to induce cell cycle which it may cause apoptosis program. The secondary metabolites are affect the differentiation and proliferation of cells by the control of intracellular (ROS) reactive oxygen species on the electron transport chain and other metabolic pathway. These cytotoxic natural products play a vital role in breast and osteo cancer. The influences of anticancer activity were valid by *Elaeis guineensis* methanol extract against MCF-7 and vera cell line through by MTT assay. The presence of apoptotic bodies could also understand in plant extract treated cancer cells. The cells are also showed extensive vacuolation in the cytoplasm, indicating autophagy like mechanism of programmed cell death.¹⁷

4. In-vivo antiproliferation mechanisms

Sreelatha et al¹⁸ (2011) study demonstrates the ethanolic leaf extract of *Sesbania grandiflora* has potential activity against anticancer. The standard criteria of anticancer drug are suppress the protein synthesis metabolism as the same induces apoptosis function of the cells. However the treatment of *S. grandiflora* extracts were control the tumor cell volume and number of viable tumor cell. The minimum dose of *S. grandiflora* 200 mg/kg have been exhibit high activity against leukemia cells which may due to its extract and it contains nature composite of various phytochemicals that could counter act its toxicity.

Eucalyptus extract curiously decreased the tumor growth rate and enhanced the life span of EAC behavior mice. The development of normal transcriptional function of tumor bearing mice has been considered as a very significant role of EAC as anticancer drugs. The Eucalyptus extract treatment group of animals were enhanced the production of macrophages in which stimulate other apoptosome molecules such as tumor necrosis factor (TNF), interleukine (IL).¹⁹ Raihan et al²⁰ (2012) proved that the methanolic extract of Lagerstroemia indica at its maximum dose 40 mg/kg can reduces the growth of tumor adequately, as well as tumor weight and increase the normal cell division function. Significantly cytotoxic activity shown by L. indica can be attributed mainly to phenol, flavonoids and gallic acid. The mangostin fruit pericarp extracts has been exhibited the most effective for antineoplastic mechanism through an induction of cell suicide mechanism in tumor cells. Human colon cancer DLD-1 cells was treated by mangostin extract it was exposed the antiproliferative effect of major xanthones. It was associated with cell cycle, by affecting the expression of cdc2, cyclin kinases and p27. The active form of xanthones called as a and bmangostins were to stimulate cell cycle arrest at the G1/G0 phase. In addition prenyl group of prenylated xanthone is

attributed to the cellular internalization, while leads to interact with signal transduction molecules and proteins involved in mitochondrial pathway.²¹

5. Plant derived secondary metabolites control the proliferative cells

Plant derived chemical substances such as primary and secondary metabolites are involved in the anticancer mechanisms especially control as well as prevent the abnormal functions in cell division (Table 1). The mainly isolated bioactive metabolites is vast such as alkaloid, flavonoids, steroidal Saponin, enzymes and terpenoid are responsible for the regulation of normal metabolic action of cells.²² Different natural bioactive compounds used cancer therapeutics was expressed in Fig. 1.

5.1. Flavonoids

5.1.1. Anthocyanins

Numerous flavonoids have been isolated from plant resources as antitumor drugs. Anthocyanin the compound analog to inhibit the cell growth in tumor cells including human lung carcinoma and leukemia cell lines. The flavonoid derivative analog derivatives are one of the important approaches for cancer chemotherapy; that is to regulate cell-cycle progression. G1/S cell-cycle arrest was found in human hepatoma, breast and colon carcinoma cells upon treatment of pigment compound anthocyanidine.²³ Flavones: Flavone 3-ols is a synthetic derivative of the flavonoid compound with special characteristics to treat of various cancers. The unique compound induces the nitric oxide synthesis it may act as cellular signaling for apoptosis mechanisms.²⁴ Quercetin: The plant derived Quercetin has been demonstrated in the action of cell culture and in human DNA. The phase III trail in used to study intraperitoneal doses of mice of quercetin has been found to have antitumorogenic effect. However Quercetin was found to down regulate expression of p53 protein to nearly undetectable levels in human breast cancer cell lines.²⁵ Cisplastin: Cisplatin has established to be one of the efficient drugs for cancer, because it targets the multiple intracellular sites, in

Table 1 – Plant derived metabolites and its activity in different cancer cell lines.					
Plant name	Materials	Functional compound	Cell line used	Mode of assay	Activity
Garcinia mangostana	Pericarps	Alpha mangostin	Colon adenocarcinoma NL-17	LDH cytotoxicity assay	Retards the growth of cancer cells
Impatiens textori	Whole	Crude compound	Human cervical/colon cancer cell	Cell viability assay	Inhibit alpha glucosidases
Inula graveolens	Whole	Flavonoids, phenolics	MCF-7	Sulforhodamine B assay	Antineoplastic mechanisms
Inula viscosa	Whole	Inuviscolide, viscic acid, xepetin	Human cervical cancer	MTT assay	Exhibit the antiproliferation function
Ononis hirta	Whole	Crude compound	HEp-2, MCF-7 cell line	MTT assay	Induction of apoptosis
Origanum majorana	Leaves	Crude compound	Fibrosarcoma (HT-180)	MTT assay, fluorescence microscopical study	Induces apoptosis
Uncaria tomentosa	Whole	Alkaloids	Human medullary thyroid carcinoma cells	Cell viability assay, DAPI — stain	Reduction of proliferation



order to induce death in malignant cells. In order to increase the efficiency of cisplatin functional analog, other drugs are used for synthetic combination.²⁶ Curcumin: Curcuma longa L. the plants have long historical background which is not only dietary supplement and also it contains more valuable therapeutic compounds. Curcumin is a polyphenol compound act as broad spectrum antibiotics including anticancer and antiinflammatory agent. The polyphenolic compound curcumin inhibits proliferation of cancer cell line through regulating numerous intracellular signaling pathways by secreting of transcription factors (TF), growth factor receptors, cell surface adhesion molecules and protein kinases. It is now under the phase III trial in mainly by the treating of pancreatic cancer. Apigenin: The apigenin phytochemical constituents mainly induced cancer cell death is mediated by androgen receptor. The prostate cancer cell line and breast cancer cell line was chosen as study models because they both express only ERb. The growth-inhibitory action of flavonoid based compound apigenin on these cancer cell lines was studied in the presence or absence of small interfering RNA (siRNA) mediated down regulation of the receptor.²⁷

Pomiferin: Pomiferin is a prenylated isoflavonoid isolation from the plant *Maclura pomifera*. Isoflavones have been shown to possess a strong activity against anion exchange scavenging activity and also to inhibit the oxidative DNA damage. Pomiferin has exposed pro-apoptotic effects by the results of DNA fragmentation. The translational studies, it was shown that pomiferin leads to down regulation of cytokeratins and to express of known tumor related proteins. **Harringtonine:** Harringtonine is chemical compound isolated from Chinese medicinal plant *Cephalotaxus harringtonia*. Harringtonine chemical entities have most promising activity against leukemic cancer cell line. The alkaloid nature of this compound induces the apoptosis of cancer cells by inhibiting protein synthesis at the ribosome level. Homoharringtonine as a plant derived chemical compound under phase III clinical trials for the treatment of patients with affected chronic myeloid leukemia (CML). **Salvicine:** Salvicine used as the antiproliferative effects by acting as a non-intercalative topoisomerase II inhibitor that induces apoptosis. Salvicine has entered phase II clinical trials for the treatment of solid tumors in various ongoing researches.²⁸

5.2. Polyphenols

Punicalagin: These punicalagin (plant: *Punica granatum*), shows inhibition of DNA topoisomerase II in transcription mechanisms. The chemical nature of punicalagin which is contains an endocyclic α,β -unsaturated ketone group, it was act more cytotoxic towards KB cells. **Phenolic acids:** The phenolics are different compounds such as phenolic esters, methyl derivatives and phenolic acids to use in various therapeutic and commercial applications. Phenolic esters mainly investigated for their antitumor activity in human adenocarcinoma cell line, also propyl and octyl gallates showed a more effective activity against HeLa cells.²⁹

5.3. Alkaloids

Campothecin: The alkaloid campothecin isolated from the Chinese traditional plant *Camptotheca acuminate*. It is used in the treatment of gastric, rectal, colon, and bladder cancers. Their synthetic derivatives 9-aminocamptothecin, 10-hydroxycamptothecin as well as camptothecin were vastly used to treat various type of cancer.³⁰ **Vinca alkaloids** (vinblastine, vincristin): Isolated of two important anticancer

alkaloids vinblastine and vincristine from the plant of *Catharanthus roseus* are well studied, these two natural alkaloids are major use of drugs in the treatment of lymphoma and leukemia respectively.³¹ **Colchicine:** The antimitotic alkaloid colchicine was isolated from *Colchicum autumnale*. The plant has been traditionally treating of gout and fever. Recent findings novel metabolites colchicine has revealed to control the tubulin binding action. **Indirubin:** Indirubin is an antileukemic compound isolated from the leaves of *Indigofera tinctoria* which is mainly used in the treatment of chronic myelocytic leukemia.³²

5.4. Saponins

Diosgenin: Diosgenin is a steroidal saponin produced by many plants. The diosgenin, purified from the root of *Polygonatum zanlanscianense* Pamp., that compound will leads to cell death of tumor cells with moderate concentration. In cell culture experiments with HeLa cervix carcinoma cells diosgenin induced apoptosis in intrinsic pathway. It control the anti-apoptotic protein Bcl-2 together with caspase activation was observed. This compound was also isolated from rhizomes of *Smilacina atropurpurea*. It stimulates the cytotoxicity on cancer cells with minimal side effects.³³

5.5. Terpenoids

Paclitaxel: Paclitaxel is a complex structure of diterpene isolated from the bark of *Taxus brevifolia*. The cytotoxic activity of Paclitaxel against mouse leukemia was well studied. It mainly involved in cell cycle mechanisms for induces disruptions of microtubule in tumor cells.³³ **Combrestatin A4:** The Flavanoids and its derivatives are also inhibit many enzymes that are the targets in anticancer treatment, e.g. eukaryotic DNA topoisomerase I, Cox I and II and estrogen 2- and 4-hydroxylases. Flavonoids by interacting with P450 enzymes reduce the activation of procarcinogen substrates to carcinogens which makes them anticancer substances in cancer therapy. **Podo-phyllotoxin:** The plant derived podophyllotoxin is a bioactive component of *Podophyllum pelatum*, and *P. pleianthum*. Its main functions involved in mitotic cell division by binding reversibly to tubulin and inhibiting microtubule assembly.³⁴

5.6. Volatile oils

Thymoquinone: Thymoquinone (TQ) is the bioactive constituent under the category of volatile oil. The compound is isolated fromblack seed (*Nigella sativa*). TQ has been reported to have potent anticancer and antioxidant abilities in both animal models and cell culture systems. One of the most favorable effects of TQ is that it exhibits high cancer specificity and low toxicity to normal cells. TQ has been highly sensitivity to prostate cancer, colon cancer and skin cancer. Many multidrug-resistant variants of human pancreatic adenocarcinoma, uterine sarcoma, and leukemia were found to be sensitive to TQ.^{35,36} The important anticancer metabolites chemical structures were described in Figs. 2 and 3.

6. Antioxidant vs proliferative cells

Antioxidants are compounds, enzymes or it may metals (non enzymes) that involved in the system auto oxidation mechanism by preventing the formation of free radicals.³⁷ Oxidative stress and reactive oxygen species (ROS) intermediated to cell



Fig. 2 – Structural analogues of important plant-based anticancer drugs.



damage have been associated with the development of human dangerous diseases such as certain cancers, neurological disorders, atherosclerosis and cardiovascular diseases. At the biochemical mechanism of antioxidants in cellular level cells are expose to oxidative stress which in turn causes the highly affected in anabolic and catabolic pathways including amino acid catabolism, protein oxidation, lipid peroxidation, other cellular inner membrane disruption and DNA damage.^{38,39} Plant derived antioxidant compounds can activate the cellular signaling networks that stimulate the normal cell division function that are observed in abnormal cells. This includes phosphorylation process leading to the activation of enzyme receptor switch on and off mechanisms, kinase and phosphatase enzymes activities, induce the gene expression level, inflammation and cancer. Oxidative regulation in tumor cells may have a strong wave on the host system to response against malignant deposit. The plant crude or purified compounds have been highly potential activity in cytoprotective and genoprotective effects against oxidative stress and it control the free radical formation in electron transport chain and other metabolic pathways.⁴⁰

7. Plant mediated nanoparticle control the tumor cells

The proper methods of immunization against tumor understandably have not yet found. But the revolution of nanopharmaceutics to synthesize the novel nanodrug carrier and specific site of action has been high effect against malignancy cells.^{41,42} Potentially prove the biosynthesized nanoparticles as good effective drug materials for cancer. Particularly piper longumine and piper longuminine act as capping agent for synthesis of silver nanoparticles and it enhance the cytotoxic effect on Hep-2 cell line. Piper longum plant synthesized nanomaterials have significant cytotoxic effect (94%-500ug/ ml) against invasive cells.⁴³

8. Pathway of cancer and genomic expression

8.1. P⁵³ gene expression

The P53 or TP53 tumor suppressor gene is the most frequently changes gene in cancer. The p53 protein is a transcription factor (TF) involved genome function by regulating cell death mechanisms and progression of cell cycle. Accordingly mutation of p53 is often difficult to treat and diagnosis is poor to identity malignancy. The p53 tumor protein contain sequence specific transcription factor, to stimulate cell growth arrest or apoptosis. These cellular mechanisms is influenced by many factors, including physical, chemical response, physiological stress and the action of p53 co-factors, p53 induces wide network of signals that act through two major apoptotic pathways.⁴⁴ They are intrinsic and extrinsic pathways.

8.2. Extrinsic pathway

The extrinsic apoptotic pathway (death receptor pathway) generates to activation of a caspase reaction by caspase regulators. The death receptors mechanism are involving various member of receptor gene family such as tumor necrosis factor (TNF), Fas R and Apo 3L. That molecules are stimulate the



Fig. 4 – The mechanism of apoptotic signaling pathways.

activity of these pro-apoptotic proteins or activate these receptors are currently their therapeutic prospective of cancer, including hematologic and hepatic malignancies. The signal transduction of the extrinsic death receptor pathway involves several caspases (family of cysteine proteases) which are specific to cellular targets. Caspase is cascade mechanism, once activated caspases stimulates several cellular function as part of a process that called as programmed cell death/ death of the cells.⁴⁵

8.3. Intrinsic pathway

The intrinsic pathway (mitochondrial) regulates the Bcl-2 family gene and BH evolutionary protein towards antiapoptotic mechanism, the formation of triggered by the cytochrome c from the mitochondrion. The impact of the apoptotic pathway may boost up the p53 target genes especially Bid, Bcl-5. The mainstream of the apoptotic mechanism are mediated to stimulate the specific target gene in cell suicide function.^{46,47} Conversely p53 can also stimulate apoptosis cell suicide function by a post transcription mechanism in which certain physiological conditions are met. Also these tremendous functions of p53 constituents in apoptosis function may highly focused in cancer gene therapy.⁴⁸ (Fig. 4).

9. Conclusion

The cancer and its mechanisms to induce the apoptotic cell function are vast studied. Hence different plant and secondary metabolites involved in the stimulate the cell suicide functions. Recently, the molecular drug development to cancer drug analog has facilitated and well designed for targeted site action in cancer therapies. The newly emerged development of the molecular characterization of cancer studies and evolution to makes it promising to develop more effective plant based drugs, and also technical supportive to monitoring the cancer cells pathway. The plant derived anticancer agents are mainly controlled the various cell mechanism in different stages of cancer such as:

- i) methyl transferase inhibitors
- ii) mitotic disruptors
- iii) DNA damage or pro antioxidant drugs
- iv) HDAC inhibitors (HDACi)
- v) inhibit the topoisomerase II action and so on.

10. Summary

The abundant results and ethnobotanical evidence suggests that plant and its compounds have beneficial effects against various cancers. Antineoplastic potential of phytochemicals that it is partially mediated through their ability to neutralize the body functions and also repair DNA damage, subsequent control the free radicals formation. There is now a great conscious in the developing of plant based drugs to against cancer and related diseases. Hence those kind of natural materials repair the cell damage and induce the normal metabolic function of the cells. Recently the great interests to developing novel plant purified product have been triggering the apoptotic program. The common impacts of tumors have defects in the p53 pathway and many overexpresses of different proteins such as Bcl-2, Box and BH3 or their close relative enzymes. According to the cluster mechanisms of apoptotic machinery remains fail to function in cell death clock. Especially, the plant derived drug that could have bind to the pro-survival protein by in which controls the cancer cells and inactivate further protein synthesis mechanisms. Nowadays cancer prospects are upbeat for the findings the mechanisms of tumor and novel drug analog for cancer and

treatments. Cancer treatment and preventing methodologies are still challenge for traditional conceptions of disease. Likewise the demanding to the development modern plant derived anticancer compound is more important for cancer control. The broad containment strategy for cancer might target all stages of disease progression. Effort to exploit on the emerging prospects of plant derived drug to treat cancer will profit significant benefits for patients as well as to those engaged in the field of drug development.

Conflict of interest

All authors have none to declare.

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