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Review Article

The Effectiveness of Anti-Cancer Compounds Taxol Derived from Natural Products from Nepal

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Abstract

Natural products play important role for medicinal therapies based on its chemical constituents, crude or in extract form. Primarily it's an effects of metabolic impact on immunotherapy for various cancer and mutli drugs effect on biotic components (bacteria and fungi). The crude extracts can be active in dual form in the body due to its polarity of constituent compounds they have high demand in pharm market as of biosynthetic capacity. Brine shrimp test and MTT assay can detect the different compound in the extracts. Taxol extracted from *tauxus brevifolia* found to be have highly toxicity for the ovarian and breast carcinoma. Apoptosis is activated by cytotoxic affect results into the diffraction of dsDNA. Further study is needed based on transcriptomics of natural products extracted from herbal medicine development.

Keywords: Natural Product; Metabolites; Taxol; Brine Shrimp; Transcriptomics and MTT Assay

Introduction

When a compound shows toxin or poison to the cells, it is referred as cytotoxicity and the compound is cytotoxic compound. Cytotoxic compound have an effect on the cells like cancer cells. Natural products can play important role for chemotherapy [1]. They have their own medicinal values for health care in human and animals. They are generally products of microbes, plants or animal sources (Nakanishi, 1999). Plants can synthesize primary and secondary metabolites. Secondary metabolites or derivatives of natural products may be used for medicinal proposed [2]. Medicinal plants have diverse structural array of the compounds in various chemotherapic natures in the crude form. The treatment of various diseases and the actualization of a non-toxic effect of medicinal remedies depend on metabolic pathways of various organs in the body. Similarly, due to different polarity of solvents and active chemical constituents of crude plants extracts (Eloff, 1998 Kotze and Eloff, 2002), there may be various influence of the toxicity of the plant extracts. If the extracts of plants have metabolically toxin activity it would affect antagonistically to the fungal cells, animal cells and bacterial cells. Researches indicate that the plant derived natural products along with microbes associated products are adversely used for immunotherapy of cancer diseases (Dahanukar., *et al*. 2000). Natural products based anticancer drug discovery is mostly interesting and active area of research throughout the world [3].

The secondary metabolites of the plants are generally alkaloids, terpenes, phenolic compounds and cyanogenic glycosides (Summener, 2000). Mostly water is used as solvent for plant extraction but polar and non-polar compounds constituents of the plants can be extracted in methanol, acetone, DCM, DSMO and Hexene for bioactivity test (Eloff, 1998c). Due to depending on the polarity of the solvents the quantity of the plant crude extract is various that may be used for beneficial or harmful to biological system. Generally, hexane is used for extraction of waxes, fats and fixed oil while acetone extracts alkaloids, aglycones and glycosides. Similarly, Methanol extracts sugar, amino acids and glycosides and DCM as well as DSMO is used for extraction of alkaloids, aglycones and volatile oils (Houghton and Raman, 1998).

Cytotoxicity through the brine shrimp test is studied in order to reveal new anticancer compounds (Harborne, 1998). The study proved that toxicity to brine shrimps responds good correlation with cancer activity mammalian system [4]. Taxol (Figure 1), the anticancer compounds, products of bark of *Taxus brevifolia* is discovered from brine shrimp test. Simultaneous cytotoxicity testing provide information of the test substances on pathogenes by using different test systems. Nowadays varieties of bioassay like animal cell line culture, MTT Assay are available for exploring different kinds of compounds (Hostettmann, 1991). There are well known anticancer drugs that directly or indirectly developed from different plant species [5]. The popular drugs are Vinblastine and Vicristine (figure 3) from *Cathanthus roseu.* Plants made medicines are highly demanded in the hospital market now because of its high biosynthetic capacity, low production cost, easy scale up; enhance safety and ability to serve as oral delivery vehicles. This review intends to explore findings of cytotoxicity compounds against cancer diseases throughout the world.

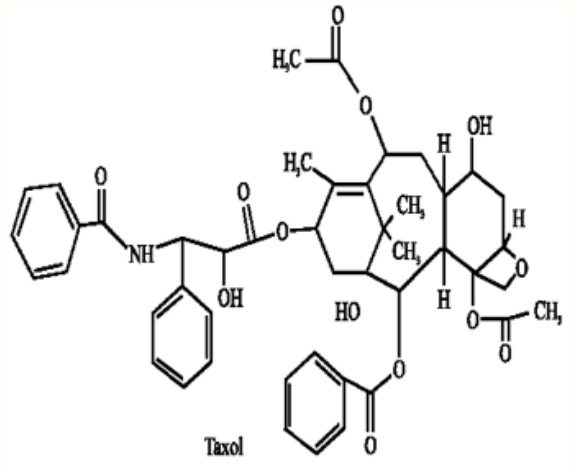

Figure 1: Structure of Taxol.

Methods

This review of the article was studies based on the specification of identification of cytotoxicity compound by the cytotoxicity assay from brine shrimp test; cell lines culture and MTT assay articles.

Discussion

Natural products in cancer therapy

Plant derived compounds have great significance to cancer therapy [5]. When the compounds Vicristine and Vinblastine (figure 3) isolated from *Catharanthus roseus*, Apocynaceae (Johnson., *et al*. 1963) was added to Mechllorethamine, prednsion and procarbazine, there was achieved first cures in Hodgkin's disease (De Vita., *et al*. 1970). Similarly the compound etoposide (figure 2) was the most active agent against fight to cell lung carcinoma [6].

Nutrient (%)	Sorghum straw	
	Healthy (T_1)	Diseased (T_2)
Proximate principles		
DM	90.75	87.56
OM	93.78	93.93
CP	05.40	03.91
EE	00.99	01.00
CF	33.05	38.20
NFE	54.34	50.82
Total Ash	06.22	06.07
Fibre fractions		
NDF	66.96	69.57
ADF	47.59	48.86
Hemi-cellulose	19.37	20.71
Cellulose	35.03	38.41
Lignin	10.17	09.03
Silica	02.39	01.42

Table 1: Proximate composition and fibre fractions (% DM Basis) of healthy and diseased sorghum straw on DM basis.

The taxol compound has been extracted from the bark of *Taxuux brevifolia*, *T. Canadensis*, *T. wallicina* or *T. baccata* belong to family Taxaceae (Wani., *et al*. 1971) and the compound camptothecins has been derived from the bark and wood of the Nyssacea family *Camptotheca accuminata* (Wall., *et al*. 1966) which have highly toxic effect on the tumor ovarian and breast carcinoma. Again these compounds have also highly active effective cytotoxicity against non small lung cancer (Mc Guile., *et al*. 1996).

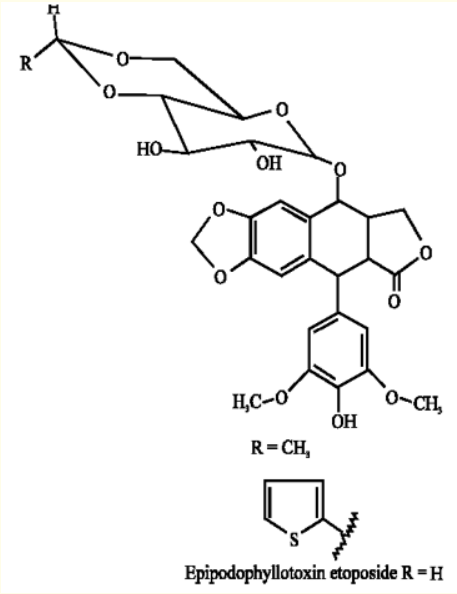

Figure 2: Structure Epipodophyllotoxin etoposide.

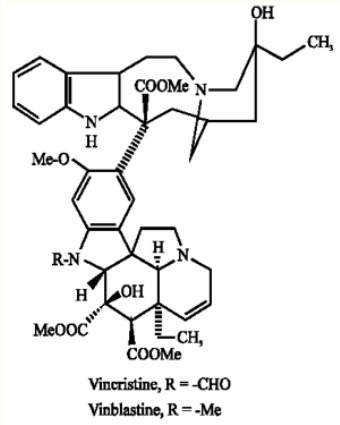

Figure 3: The structure of Vincristine (R= -CHO) and Vinblastine (R= - Me).

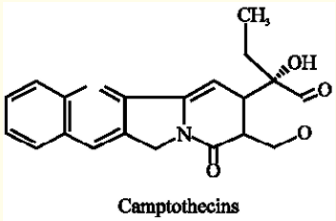

Figure 4: The structure of *Camptothecins*.

Biological assay

Natural plant products chemistry must be in cooperate with biological assay for biological activity or to know that particular characteristics of the extracts [7]. Different researchers have been performed various test for analyze chemical constitution effect of the plants on animal cells, fungal cell and bacterial cells. The toxicity of the plant extracts can be evaluated by following test in which do not required higher animals to screen [7]. a) the brine shrimp lethality test (BST), a general bioassay) and b) the inhibition of crown gall tumor on of potato tubers (an anti-tumor bioassay). Regarding the Brine Shrimp Lethality Test (BST), different concentration of the plant extracts has been practice for toxicity test to *Artemia salina* larvae. Toxicity to *Artemia salina* larvae has a good correlation with the anti tumor and pesticides [4] and antitrypanosoma (Zani., *et al*. 1995). The DNA-dependent RNA polymerases of *A. salina* larvae has been observed to mammalian one (Brindorf., *et al*. 1975). Similarly, Chemical extracts of natural products have been cytotoxicity test practiced nowadays through MTT assay and cell line of animals.

Cytotoxicity effect of the extract through Brine Shrimp and cell lines

According to Fiot., *et al*. 2006, the alkaloids extracts Guieranon A (Figure 5) of leaves and roots from *Guinera senegalensis* have cytotoxicity affect against to the human monocytes (THP1 cells); two cancer cell lines (human cervix and human colon carcinoma) and normal skin fibroblasts during *in vitro* study. Furthermore, the isolated of total cardiac glycosides and total sesquiterpene lactones from the leaves ethanolic extract of G. senegalensis observed cytotoxicity to the brine shrimps by Dahawi in [9].

Figure 5

Again the new compound Trachlobane diterpene (Figure 6) was found by Block., *et al*. [8] in 2002 from the leaves of *Croton zambezicus* (Euphorbiaceae) which have high toxicity to the animal cells and another research revealed that the flavonoid extracts of seeds of *C. zambezicus* showed high toxicity to Brine Shrimp [9].

Figure 6

It was reported that the isolated chelerythrine from the root of *Argemone mexicana* belongs to papaveraceae found to exhibit significant activity against human gastric cell line (NUGC) while angoline inhibited NUGC and human nasapharyngeal carcinoma (HONE-1) [10]. But Chang., *et al*. [11] in 2003 explained that the Argenaxine compound extracted from leaves of *A. mexicana* showed moderately activity against the NUGC cell lines and also in the brine shrimp test, the ethanolic extracts of leaves, seeds and roots from same species have high toxicity [9]. It was reported that the ethanolic extract of *U. dioica* has capacity to cytotoxic effect on T47D cell line with 46.14 ± 4.55 µg/ml IC50 value. Simillarly, the ehtanolic extract of the dried fruit pericarp of *Punica granatum* L. belongs to family Punicaceae was founf to bemore toxic to the brine shrimps in BST [9,10]. According to Ghisallberti (2000), *Lantana camara* L. belongs to family Verbenaceae is evergreen strong smelling herb [12] showed diverse biological activities including cytotoxic and anticancer properties. Also it was reported that the leaves methanolic extract of *L. camara* has moderate activity against Dalton's lymphmma Asciites (DLA du to the presence of toxic lantanoids e.g. Lantadene A (figure 7) and lantadene B (Figure 8) [13].

Figure 7

Figure 8

The chemical compounds extracts from plants are varied to varied solvents and plant species. In most cases, the highest quantity of extracts was obtained in methanol and followed by ethanol, acetone and hexane [9]. According to Neerugatti., *et al.* [14] reported that the methanolic extract of *P. semierectus* showed more cytotoxic activity on cell lines compared to the other solvent extracts. The high yield extracts obtained may be presence of polar compound in selected plants. The biological activities of the plant extracts are depend on not only the solvent used but also impact by morphological stages of the plants. It may be correlated with the season of the year with containing storage of carbohydrates in it. Such a similar report was reported by Siddiqui., *et al*. in 1986 and Naqvi *in 1987* that the isolated of nimocinolide (Figure 9) and isonimocinoide (Figure 10) from young leaves of *Azadirachta indica* belongs to family Meliaceae showed high larvicidal properties when applied to larvae of *Aedes aegypti* and similarly it was also reported that the ethanolic extracts of young leaves of *A. indica* in winter showed high cytotoxicity in the brine shrimp test compared to the mature one [9].

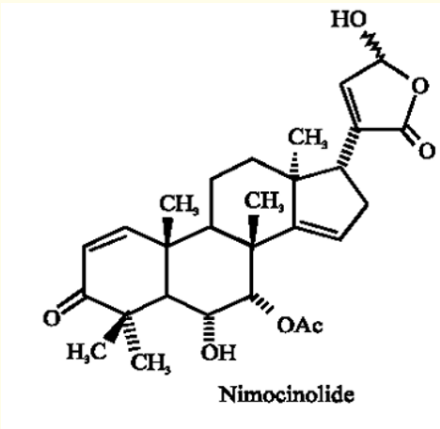

Figure 9

Figure 10

The various concentration ranges of the plant extracts show the various toxic effects on the cells. Generally the lowest concentration of the plant extract observed least toxic effect on the Brine shrimp test [9,15]. However the cytotoxicity of the medicinal plant extracts should not only effect dose by dose but also the function of pharmacology, chemistry, metabolism, environmental and genetic risk factors (Li, 2004). But the investigation of the toxic effect of crude medicinal plant extracts drug-drug interaction based on pharmacological properties can play safety or cytotoxic effects *(*Koppa, 2003). Although in some studies brine shrimp assay has been reported to demonstrate some correlation with cell line results for detecting cytotoxic compounds/extracts [16,17].

Cancer cell line was useful to observe to response of action on cells [18]. Mahavorasirikul*., et al.* [19] has studied the extract of *Buchanania axillaris* Desr, *Tamilnadia ulignosa* Retz, *Phaseolus semierectus* L and *Stylosanthes fruticosa* Retz on HT-29 cell lines for colon cancer, MCF-7 and MDA-MB cell lines for breast cancer. They have reported that the extracts of *T. ulignosa, P. semierectus* and *S. fruticosa* showed the more activity on the MCF-7 cell lines and HT-29 cell lines but surprisingly *B. axillaris* extract showed the better activity on MDA-MB cell lines. But among all tested plants extracts *P. semierectus* showed the better cytotoxicity activity on tested cell lines. The cytotoxicity of the medicinal plants is caused due to the apoptosis or necrosis of cells [20,21]. Apoptosis have cell shrinkage, activation of caspases, DNA cleavage, chromatin condensation, and nuclear fragmentation [14]. During apoptosis, activation of endonucleases breaks down double-strand in DNA between nucleosomes leading to that DNA. And it is fragmented into multiples less than 200 base pair pieces [22].

Mahavorasirikul., *et al.* [19] has been reported that the ethanolic extracts from seven plant species (*Atractylodes lancea, Kaempferia galangal, Zingiber officinal, Piper chaba, Mesua ferrea, Ligusticum sinense, Mimusops elengi*) and one folklore recipe (*Pra-Sa-Prao-Yhai*) showed strong activity against the cholangiocarcinoma (CL-6) cell line with survival of less than 50% at the concentration of 50 µg/ml. Kasani., *et al*. 2014 have concluded that the ethanolic extract of *Utrica dioica* showed the potent cytotoxicity activity against breast ductal carcinoma (T47D) cell line with IC 50 valuse of 46.14 ± 4.55 µg/ml. The alcoholic extract of *Ocimum sanctum, Calotropsis procera, Canabis sativum, Trigonella foenum* showed high cytotoxicity activity on the cell line, human neuroblastoma (IMR-32), Lung cancer (A-5409), Colon (H-15 and H-29) but the ethanolic extract of *Chenopodium rubrum* showed cytotoxocity activity against to the cell lines of Colon (H-15 and H-29) only [15]. Sarkar and Mandal [23] have reported that the Hydroalcoholic extracts of *Terminalia chebula, Terminalia belerica, Emblica officinalis, Caesalpinia crista, Cajanus cajan, and Tinospora cordifolia* were found to be variably and selectively cytotoxic effect on murine tumor cell Ehrlich's Ascites Carcinoma (EAC) and non toxic in normal spleenocyte cell. In addition, it was reported that the hydromethanolic extract of *Lavandula antineae* has showed

good toxic against brine shrimp nauplii, with IC_{50} of 13.72 µg/ml. Actually, the degree of cytotoxocity was found to be directly proportional to the concentration of the crude extract. According to Meyer., *et al.* [16] a crude plant extract is considered as toxic (active) if an IC_{50} value is of less than 1000 µg/ml. Indeed the different crude extracts of plants have toxicity differently to cell/organisms in various levels on the basis of route of consumed due to the biological activity of the organisms on crude extracts. Kang., *et al*. (2008) reported that aqueous and ethanolic leaf extracts of *Antiaris toxicaria* have non toxic to mice even at high doses when given orally. But, when high dose of extracts was administered by intra-peritoneal route it showed toxicity.

A.K. Azad., *et al.* [24] have concluded that different concentration of the ethanolic crude extracts showed effective cytotoxicity on Brine Shrimp and cell line, if plants have toxic chemical compounds. They have demonstrated that the ethanolic extract of three medicinal plant species i.e. *Uncaria acida, Leea indica* and *Piper porphyraphyllum* have exhibited highy active cytotoxicity on Brine Shrimp and Cell line of MCF-7. Similarly, the ethanolic and methanolic extracts of *Ambrosia ambrosiodes* [25,26], *Gutierrezia microcephala* (X.-P.Dong., *et al*. 1987) and *Atriplex confertifolia* [27] have been showed actively cytotoxicity on the Hella cells. According to Gary M. Booth., *et al*. [28], the extracts of mints family *(Labitae)* have also effective cytotoxicity on Hella cells [29-47].

Conclusion

The cytotoxicity effect is directly proportional to the extract composition and depend upon the growth time and environment condition of the plant, even the solvent alter the effectiveness of the crude extract. The crude extract have high impact on HeLa cell lines. The Assay shows a coordinate for the degree of cytotoxicity was found to be directly proportional to the concentration of the crude extract, which directly activate apoptosis due to the defragmentation of the dsDNA. The precise composition and chemical characterization of active compounds is need to be explored for further research analysis.

Conflict of Interest

The authors declare that they have no conflict of interests.

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