

Anticancerous potentials of *Nothapodytes nimmoniana* (grah.) Mabb -

A review

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Abstract

Cancer is one of the most prevalent diseases in many countries worldwide. Cancer harms the body when altered cells divide uncontrollably to form lump of tissues called tumors. Most treatment plans may include surgery, radiation or chemotherapy. An integrated approach is needed to manage cancer using knowledge gained through scientific developments. According to the World Health Organization (WHO), about three quarters of the world's population currently use herbs and other forms of traditional medicines to treat diseases. *Nothapodytes nimmoniana* contains camptothecin as its active constituent which is used in the treatment of cancer in traditional systems of medicine. Camptothecin (CPT), a monoterpene indole alkaloid, is regarded as one of the most promising anticancer drug of the 21st century. Hence this article discusses about the anticancerous activity of *Nothopodytes nimmoniana* and its phytoconstituents on various types of cancer cells.

Keywords: *Anticancerous, Nothapodytes etc.*

A BRIEF SUMMARY ON CANCER

Cancer is one of the most prevalent diseases in many countries worldwide. The current Indian population is 1,270,272,105 (1.27 billion). The incidence of cancer in India is 70-90 per 100,000 population and cancer prevalence is established to be around 2,500,000 (2.5 million) with over 800,000 new cases and 5, 50,000 deaths occurring each year [1]. It is characterised by uncontrolled and irregular proliferation of cells. The exact cause is mysterious, but inhibition of the defence mechanism responsible for the elimination of disturbed cells is generally accepted as a background of carcinogenesis, but inhibition of the defence mechanism responsible for the elimination of disturbed cells is generally accepted as a background of carcinogenesis.

PATHOLOGY OF CANCER

Cells are building block of living things. Apoptosis is most finely coordinated regulatory functions for maintenance of the homeostasis in the living organism. Morphologically there will be nuclear condensation, cell shrinkage, membrane blebbing and the formation of apoptotic bodies. A cancerous tumour has the capacity to grow rapidly and to metastasize or spread to other tissues. Some tumours like leukaemias grow as cell suspensions but most grow as solid masses of tissue. Cancer can develop in any organ such as lung, colon, breast, nerve tissue and other parts too. According to Indian Council of Medical Research (ICMR) data on site specific cancer burden, in males, the most common are cancers of mouth/pharynx, esophagus, stomach, lung/bronchi while as in females, the common cancers are cervix, breast, mouth/oropharynx and esophagus.[2]

Modern treatments include chemotherapy, immunotherapy, radiotherapy etc which have made vast progress in cancer treatment but the side effect is also making the patients suffer a lot. An integrated approach is needed to manage cancer using knowledge gained through scientific developments.

NOTHOPODYTES NIMMONIANA: A BRIEF ACCOUNT

Over 50 % of all modern clinical drugs are of natural product origin. [1] Although more than 1500 anticancer drugs are in active development with over 500 of the drugs under clinical trials, there is an urgent need to develop much effective and less toxic drugs the plant kingdom plays an important role in the life of humans and animals.

According to the World Health Organization (WHO), about three quarters of the world's population currently use herbs and other forms of traditional medicines to treat diseases. *Nothopodytes nimmoniana* (grah.) Mabb earlier known as *Mappia foetida* are mostly used for the treatment of cancer. *Nothopodytes nimmoniana* has a rich source of the potent alkaloids such as camptothecin (CPT) and it is the most potent and promising Anticancerous drug among the plant derivatives [3, 4]. *Nothopodytes nimmoniana* (J. Graham) (Icacaceae), commonly known as Amruta is found in India particularly in Maharashtra, Goa, Kerala, Assam, Jammu and Kashmir as well as Tamilnadu areas. It is popular in Maharashtra [5] The *Nothopodytes nimmoniana* vernacular names are Ghanera, Durvasane mara, Kalgur, Kalagaura. It is an important medicinal plant, the major source of a potent alkaloid, namely camptothecin, of a wide spectrum of pharmacological activities like anti-cancer, anti-HIV, antimalarial, antibacterial, anti-oxidant, anti-inflammatory, anti-fungal and also applied in the treatment of anaemia. Camptothecin contains a pentacyclic ring system that includes a pyrrol (3,4-b) quinoline moiety (ring A, B and C). Camptothecin and its derivatives are unique in their ability to inhibit DNA topoisomerase I by stabilizing a covalent reaction termed the cleavable complex which ultimately causes tumor cell death. Topotecan is water-soluble analog of the natural chemical compound camptothecin.

Hence there is a lot of inclination towards natural medicines, so an attempt has made to review about anti-cancerous activity of *Nothopodytes nimmoniana* on different types of cancer.

***Nothopodytes nimmoniana* ANTICANCEROUS STUDIES:-**

A) CELL LINE STUDIES :

1) Role in Breast cancer:

Premalakshmi et al. (2011) In 2005, breast cancer caused 502,000 deaths world wide (7% of cancer deaths, almost 1% of all deaths, WHO, 2007). A study on anti cancerous activity carried on *Nothopodytes nimmoniana* leaf, bark and root extract against MDA-MB-231 cells (breast CA cells). The IC50 of the leaf, bark and root extract against MDA-MB-231 cells are 450 and 500 µg/ml respectively. It was found that cells stained with the fluorescent dyes revealed abnormal nuclear morphology revealing both apoptosis and necrosis. The treatment with bark extract induced higher level of apoptotic death and treatment with the leaf extract induced the death of CA cells. Treatment with the root extract induced both the type of cell death at an equal ratio. The inhibitory effect on MDA-MB-231 cells was observed with Topotecan, an analogue of Camptothecin. The IC50 concentration of Topotecan was found to be 160 ng/ml in MDA-MB 231 cell line. Treatment with Quercetin enhanced cytotoxicity of Topotecan as 1,3 fold in MDA-MB231 cell line (Akbas et al., 2005). It was found that cells stained with the fluorescent dyes revealed abnormal nuclear morphology revealing both apoptosis and necrosis. Loss of mitochondrial transmembrane potential was observed in both MDA-MB23 and SiHa cells. All the three extracts led to the loss of mitochondrial potential. Mitochondria are well known as targets led to the loss of mitochondrial potential. Mitochondria are well known as targets for chemotherapeutic agents because they have a central role in the induction and regulation of apoptotic cell death (Brenner et al., 2003; Debatin et al., 2002). The treatment with bark extract induced higher level of apoptotic death and treatment with the leaf extract induced the death of CA cells. Treatment with the root extract induced both the type of cell death at an equal ratio. The inhibitory effect on MDA-MB-231 cells was observed with Topotecan, an analogue of Camptothecin.^[6]

2) Role in Cervical cancer:

Premalakshmi et al. (2011) cervical cancer is a cancer arising from the cervix. Human papilloma virus (HPV) infection appears to be involved in the development of more than 90% of cases. Worldwide, cervical cancer is both the fourth-most common cause of cancer and the fourth-most common cause of death from cancer in women. In 2012, an estimated 528,000 cases of cervical cancer occurred, with 266,000 deaths. This is about 8% of the total cases and total deaths from cancer⁽⁷⁾. The treatment of cervical cancer caused due to HPV infection can be treated with surgery, chemo and radiotherapy which have a few harmful side effects. The recurrence rate is also higher

(Souhami and Tobias, 2005). The treatment of cervical cancer cell line, SiHa, (HPV16 viral genome integrated) with the leaf, bark and root extracts of *Nothopodytes nimmoniana* showed inhibitory effect on the cells and also cell death. The mode of the cell is similar to that takes place in breast cancer i.e., Apoptosis and Necrosis. Onset of the mitochondrial permeability transition (MTP) is a key event in both necrotic and apoptotic cell death (Lemasters et al., 1998) [8].

3) Role in colon cancer:

D Arango et al(2003) The proto-oncogene c-Myc is overexpressed in approximately 70% of colorectal tumours (Erismann et al, 1985). c-Myc overexpression in colon carcinoma LoVo cells resulted in sensitisation to camptothecin-induced apoptosis, thus identifying c-Myc as a potential marker predicting response of colorectal tumour cells to camptothecin. The expression of 10 of these genes was confirmed to be significantly correlated with response to camptothecin in a panel of 30 colorectal cancer cell lines [9].

B) ANIMAL STUDY :-

1) Against Dalton's lymphoma ascites tumor :-

Senthil Rajan Dharmalingam et al (2014) *Nothopodytes nimmoniana* heartwood and barks against Dalton's Ascitic Lymphoma (DAL) in Swiss mice. Myelosuppression and anaemia is the foremost difficulties encountered in the cancer chemotherapy. DAL cells were injected intraperitoneally 1X10⁶ cell to the mice. Two days after cells injection the animals were treated with ethanolic extract heartwood and barks at dose of 200 mg/kg for 14 days. *Nothopodytes Nimmoniana* extract treatment was found to enhance nonviable cell counts in peritoneal exudates and decrease the viable cell count. It might be due to the absorption of ethanolic extract by viable cells which leads to lysis of cell through to the activation of macrophages or some cytokine production in peritoneal cavity. The present investigation showed a decrease in cancer cell count, tumour volume, RBC count as a confirmatory evidence for protection against DAL [10].

C) CLINICAL STUDIES :-

1) Role in ovarian cancer:-

H Gelderblom et al (2001) the most common type of ovarian cancer, comprising more than 95% of cases, is ovarian carcinoma. In 2012, ovarian cancer occurred in 239,000 women and resulted in 152,000 deaths worldwide. Combining cisplatin and topotecan, 2 potentially active agents in ovarian cancer in a dose-dense scheme, is attractive and giving their preclinical synergism; single agent oral topotecan is as effective as i.v., with less grade 4 neutropenia in advanced ovarian cancer (Gore et al, 1998) [11].

2) Role in lung cancer:

N Masuda et al (1998) Lung cancer is a major health care problem throughout the world. Non-small-cell lung cancer (NSCLC) accounts for approximately 75% of all lung cancers. A phase trial of the combination of irinotecan (CPT-11) with cisplatin in advanced non-small cell lung cancer (NSCLC) showed a very promising response rate of 54% in previously untreated NSCLC patients. The median duration of response was 19 weeks and the overall median survival time was 44 weeks. The 1-year survival rate was 33%. The major toxic effects were leucopenia and diarrhoea. A combination of CPT-11 and cisplatin is very effective against non-small-cell lung cancer with acceptable toxicities [12].

DISCUSSION

Cancer appears to occur when the growth of cells in the body is out of control and cells divide too quickly. It can also occur when cells forget how to die. In terms of cancer deaths, the mortality rate among men and women in India is almost the same. While 3.56 lakh men died of cancer in 2012 in India, the corresponding number for women was 3.26 lakh. One in every 10 Indians runs the risk of getting cancer before 75 years of age. There are

many different anticancer herbs that have been used by different cultures throughout time for medicinal purposes. *Nothapodytes nimmoniana* contains camptothecin as its active constituent which is used in the treatment of cancer in traditional systems of medicine. Camptothecin (CPT), a monoterpene indole alkaloid, is regarded as one of the most promising anticancer drug of the 21st century [13, 14].

Nothopodytes nimmoniana has a rich source of the potent alkaloids such as camptothecin (CPT) which has proved for its anti-cancerous activity. Topotecan (trade name Hycamtin) is a chemotherapeutic agent that is a topoisomerase inhibitor. It is a synthetic, water-soluble analogue of the natural chemical compound camptothecin. The anti-tumor activity of CPT and its derivatives is mainly due to its interaction with Topoisomerase 1 (TOP1), a ubiquitous enzyme involved in the regulation of DNA topology during replication, recombination and transcription. TOP1 forms a phosphotyrosine bond with DNA, catalyzing a forward reaction in which DNA is cleaved to allow unwinding, and a reverse reaction in which DNA is religated. CPT interferes with the religation step of this process by reversibly binding to and stabilizing the enzyme/DNA complex. Topotecan is believed to exert its cytotoxic effects during the S-phase of DNA synthesis. Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single strand breaks. This ternary complex interferes with the moving replication fork, which leads to the induction of replication arrest and lethal double-stranded breaks in DNA. As mammalian cells cannot efficiently repair these double strand breaks, the formation of this ternary complex eventually leads to apoptosis (programmed cell death). Topotecan mimics a DNA base pair and binds at the site of DNA cleavage by intercalating between the upstream (-1) and downstream (+1) base pairs. Intercalation displaces the downstream DNA, thus preventing religation of the cleaved strand. By specifically binding to the enzyme-substrate complex, Topotecan acts as an uncompetitive inhibitor. There is no direct reference regarding anticancerous activity of *Nothopodytes nimmoniana* in ovarian, lung, colon cancer. But there are studies explaining about the anticancerous activity of camptothecin and topotecan in ovarian, lung, colon cancer. Since *Nothopodytes nimmoniana* contains both phytochemical camptothecin and topotecan it can be inferred that it works on ovarian, lung, colon cancer.

CONCLUSION

Nothapodytes nimmoniana contains camptothecin which is considered as the most potent and promising anticancerous drug among the plant derivative. Camptothecin and Topotecan are proved as effective anticancerous drugs in Breast, Cervical, Ovarian, Lung, Colon etc cancers.

Studies regarding the anticancerous activity of the *Nothapodytes nimmoniana* are conducted using the particular phytochemical extract i.e., using Camptothecin and Topotecan. Therefore further exploration is required regarding its anti cancerous activity and folklore practice of *Nothapodytes nimmoniana* when drug is used as a whole.

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