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Anticancer Activity of Curry Leaf (*Murraya Koenigii*)

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Introduction

The abnormal cells divide without any control on their cell division and can grow into a mass which spread to other parts of the body, is called as cancer [1]. These cells can spread over to different parts of the body by choosing blood and lymphatic systems, which is termed as metastasis. Different types of cancer diseases severely affect human beings all over the World [1, 2]. Breast cancer is the second most prevalent cancer in the World after lung cancer, and is a major health issue in developing countries like India. Every year 75,000 new cases of breast cancer are reported in India, which demands for new therapies to treat and prevent this life threatening disease [3].

Search for new anti-cancer drugs, from natural sources is one of the most important approaches as they are considered to have fewer side effects compared to current treatments of chemotherapy. Because of the unfavorable effects of existing synthetic drugs in market, the importance of natural products has increased [4]. In recent years herbal medicine is now being explored for cancer therapy. The cancerous cells undergo mutation in their genes and in contrast to normal cells, they don't stop dividing and continue to grow with gradual increase in their size, and this uncontrolled cell growth results in the formation of a tumor [3].

Curry leaf plant

Curry leaf (*Murraya koenigii*) plant is a small aromatic tree belonging to the family Rutaceae, and this is a subtropical tree native to India. Among all its 14 global species, *M. koenigii* is said to be more popular with its large spectrum of medicinal properties. These leaves have a slight pungent smell, bitter and feebly acidulous taste which can be retained even after drying them. It

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has proven its effectiveness for many centuries in the Ayurveda field [5]. The leaves of this plant are used in different types of Indian cuisines for the aroma it has. These leaves are mixed withm main ingredients in various forms like from paste to fried leaves in oil [6]. The leaves, roots, fruits, bark etc. are the different parts of the plants which are said to have different medicinal properties. This curry leaf plant is used as medicine for stomachic and carminative in Indian tradition [7-9].

Phytochemistry of curry leaf plant

Till now, almost 88 different alkaloids, along with several other metabolites like terpenoids, phenolic and essential oils are identified from different plant parts of *Murraya koenigii* plant. Many secondary metabolites like alkaloids, flavonoids, essential oils, terpenoids etc. are having significant medicinal properties which are present in curry leaf plants, whereas the antiproliferative property is only regulated with few alkaloids and flavonoids [10]. The main constituents of the plant which are reported are flavonoids, alkaloids and coumarins [11]. The alkaloids, flavonoids and other components of this plant possess anti-oxidative [12-14], anti-diarrheal and anti-trichomonal activities [15,16]. As there are many health benefits by the usage of curry leaves and its ability to cure stomach and intestinal ailments, scientists have studied its ability to act against stomach related cancers [17].

The total flavonoid content has been determined through modified calorimetric studies. In a study performed, 20µl of leaf extract has been added to 120µl of distilled water. 7µl of $NaNO_2$ of 5% concentration has been added to the initial master mix. 5 minutes' incubation at room temperature was followed by addition of AlCl3 of 10% conc. With volume of 15µl second stage incubation was performed at 25°C and 1M in 50µl of NaOH has been added to the mixture. Further dilution was made to check OD at 510nm [18]. Other assays like antioxidant, free-radical regulating activity and enzyme assay of lactate dehydrogenase has been performed. Besides, biochemical tests like catalase, superoxide dismutase etc. has been performed. The induction of cells by curry leaves showed some changes in morphology along with some statistical analysis. The enzymatic studies have shown that the catalase activity is very high along with the increased

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activity of superoxide dismutase after 12 hours. The scientists marked the activities of leaf extract of curry leaves exhibit a determinable action against cells of colon cancer and also protective action on liver cells. The phytochemicals like polyphenols are studied and proved to be effective against cancer cell line [19]. The curry leaf extract has shown a significant effect on colon cancer cells with significantly less toxicity. The animal models have also shown the similar effect from the leaf extract. The major breakthrough has shown less ethanol dependent toxic effect in mouse model using curry leaves along with liver cell. The change in morphology implies induction of cell death (apoptosis) in leukemia, and breast cancer along with curing effects on prostate and colon cancer [20]. The ability of curry leaf extract to regulate with proteasome inhibition, helps to inhibit the growth of cancer cells [20].

Along with flavonoids, another compound that is present in curry leaf plant is mehanine. ehanine is a carbozole alkaloid which leads to the inhibition of growth in G0/G1 phase of cell cycle in glioblastoma cell line [21]. This compound is known for its cell death properties for different cancer cells. In recent understandings it has been pointed out that mehanine is the compound which can work against leukaemia cells in the body. As the PI3K pathway is the chief inducer of tumor, mehanine dependent defense system targets this specific pathway and controls the growth of tumor cells in prostate cancer along with other cancers like leukaemia [22].

Cytocidal mechanism of curry leaf extract

For the growth and survival of the cancer cells, they require a very high proteasome activity [23]. Curry leaves are the great source of polyphenols and flavonoids which inhibit the proteolytic activity of cancer cells and lead to its demise. In the hydro-methanolic extract of the curry leaves, cytotoxicity was assessed by MTT assay. This extract decreases the cell viability and alters the growth kinetics in the cancer cell lines, by arresting the cancer cells in its S phase. On treating the cells with curry leaf extract, the activity of 26S proteasome is decreased in the cancer cells only. It does not have any effect on normal cells. Unlike normal cells, cancer cells have increased proteasomal activity that is essential for its survival. Inhibition of the proteasome activity by the inhibitors of 26S proteolytic unit results in apoptosis and causes cell cycle arrest

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in cancer cells only but not in normal cells. Hence proteasome has emerged as an attractive molecular target for cancer therapy [20].

Preparation of curry leaf extract

a) Collect the curry leaves from a single tree.

b) Wash and air dry them in shade for 1-3 weeks.

c) Grind the dried leaves to a fine powder using an electric mixer grinder.

d) Extract the powder using 80% methanol with water by vortexing the mixture for 3 to 4 days.

e) Then Centrifuge the extract at 5000 rpm for about 30 minutes.

f) Filter the supernatant using a 0.2µm filter.

g) Store the resultant methanol: water extract at -20° C for any further use [24].

Phytochemical analysis of leaf extract [25]

Test for tannin

Add few drops of $FeCl_2$ in 2ml of leaf extract solution. Appearance of dark green color indicates the presence of condensed tannin.

Test for anthraquinone

2ml of leaf extract solution is heated along with chloroform and then mixed with 1ml of ammonium hydroxide. Appearance of rose red color indicates the presence of anthraquinone.

Test for glycosides

Add few drops of molisch reagent in 2ml of leaf extract solution and then sulfuric acid is added drop by drop into the test tube. Appearance of violet ring indicates the presence of glycosides. Molisch reagent – 10% alcoholic solution alpha-naphthol

Test for saponin

Add 5ml of distilled water in 5ml of leaf extract solution and then mix it vigorously. If we find foam after mixing, then it indicates the presence of saponins.

Some important plants with anti-cancer activity

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The plants with anti-cancer properties had been recognized over centuries. The isolation of lignans and podophyllotoxins from the american may apple plant (*Podophyllum peltatum*) led to the discovery of medicine for treating testicular and small cell lung cancer [26]. *Anacardium occidentale* (cashew tree) and *Gynandropis pentaphylla* (African cabbage) are used for hepatoma treatment. The *Podophyllum peltatum* (American mayapple) is used to develop drug for treatment of testicular and small cell lung cancer. *Alstonia scholaris* (blackboard tree) can be used to treat stomach carcinoma. *Boswellia serrata* (Indian frankincense) and *Paederia foetida* (Chinese fever vine) are used in treating human epidermal carcinoma of nasopharynx. *Asparagus racemosus* (shatavari) is used in human epidermal carcinoma, whereas *Nigella sativa* (black cumin) is used as therapeutics in lung carcinoma [27].

Role of *Anacardium occidentale* as anti-carcinogenic compound

The peer shaped fruit of the cashew tree was previously considered waste and was discarded. But recent studies and developments has shown that there are so many useful properties in the apple of the cashew. This cashew apple is now used in the manufacturing and production of jams, cashew apple drinks, juices, syrups, chutney and beverages [24]. There have been so many tests to examine the antitumor activity, since many prostaglandin related compounds exhibited potent antitumor activity. The preliminary screening tests has found that the cashew apple juice was showing significant (ED50<20µg/mL) in vitro cytotoxicity against BT-20 breast carcinoma cells. The anti cancer activity of cashew apple might be even more better than compared to any other product.

Shatavari

Among the most important medicinal plants, shatavari is one of them as it contains estrogen like chemical constituents called phytoestrogens [28]. Many studies signify that the extract of the root of this plant with chloroform and methanol (1:1) decreases the growth of T47D cancer cells [29]. Petroleum ether, ethyl acetate, methanol and methanol water are the four extracts of this Shatavari plant which are considered for inhibiting cancer cells [30]. Among all the four extracts,

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methanol and water extract shows impressive activity as they are the rich source of Kaempferol, genistein, Daidzein, Rutin and quercetin [31].

Podophyllum peltatum

Podophyllum peltatum, which is commonly known as American may apple, contains podophyllin and has similar action of inhibiting cancer cells like the other medicinal herbs which inhibit cancer cells. These podophyllins stop the multiplication of cancer causing cells by breaking the microtubules into smaller sub units, thus inhibiting the division of cells. The active principle of podophyllin, podophyllotoxin is used in the treatment of bronchogenic carcinoma and cancers of the ovary and the testis [32].

Conclusion

The use of modern medicine is limited by the drug resistance in cancer therapy. Whatever the practical solution which we have, to control the initiation and progression of cancer will have a great importance. The huge side effects of chemotherapy can be reduced by following natural therapy which means by using medicinal plant products we can arrest the carcinogenic process which alters the chemotherapy with less side effects. Most of the plants and herbs which we get in the forest have been evaluated in the clinical studies and are being investigated whether they have tumoricidal properties against various cancers or not. This review specially indicates that the hydro-methanol extract of *M. koenigii* has the potential to inhibit the 26S proteasome in cancer cells. This inhibition of proteasome in cancer cells is the major biological activity of any plant extract which will be used to treat cancer.

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