IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Review: Anti-Cancer Activity Of Medicinal Plants

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ABSTRACT

Globally cancer is one of the commonly life-threatening diseases which severely affect the human being. It is recognized by the uncontrollable division of cells. There is a demand for new methods to prevent this disease. Conventional therapies have several adverse effects on the on healthy cells, therefore, an alternative and effective medication are required to combat this disease. Benefits of using plants derive product over synthetic medication have increased the importance of medicinal plant in the field of healthcare. Many plants derive product shows potent in cancer treatment by inhibiting cancer activating enzymes, stimulate DNA repair mechanism, induce anti-oxidant action, and promote protective enzymes production.In the present review, an effort has been done to provide information about the various compounds present in the medicinal plants that have shown potent activity against various forms of cancer. Internationally accepted classifications of malignant tumors, developed by the World Health Organization (WHO) and the Union for International Cancer Control (UICC), are based on the histotype, site of origin, morphologic grade, and spread of cancer throughout the body TheWHO classifications are the foundation of cancer diagnosis and the starting point for cancer management. Starting in 2000, the WHO classifications began to include biologic and molecular-genetic feature.

KEYWORDS- Anticancer activity; Cytotoxic effect; medicinal plants; phytocompounds;Cancer, Classification; Cancer diagnosis; cancer management.

Cancer background-

INTRODUCTION

During this century, cancer has become one of the major problems and diseases which has caused predominant death, and it will even surpass heart diseases. Many of the researchers begin to use the term lifetime risk for cancer patients which refer to the time that cancer will progress and developed or the time that the patients will die because of cancer. Cancer does not represent only one disease but it is a group involving about 100 diseases. It is characterized by two things: Firstly there is no control for the growth of cancer cells, and secondly it is the ability of the cancer cells to metastasize and migrate from the original site to different parts of the body. There are two types of tumors which are malignant and benign. Cancer can attack any person, and its occurrence increases as the age of the individual increases too [1, 2]. There are many problems (i.e., side effects) associated with cancer diseases either solid or hematological cancer such as nausea, vomiting, diarrhea, constipation, hypercalcemia, pain, loss of appetite, anemia, fatigue, cachexia, leucopenia, neutropenia, and thrombocytopenia. However the major problems are nausea and vomiting, neutropenia, anemia, thrombocytopenia, and hypercalcemia. Hence due to these reasons, cancer is considered as one of the major diseases that will affect the quality of life [3–6].

Chemotherapy background-

Chemotherapy was developed and used since the Word War I from the chemical weapon program of the United States of America (USA). Since then chemotherapy has become as one of the most important and significant treatments of cancer. Its main mechanism of action is by killing the cancer cells which are characterized by their high multiplication and growth rate. It will also kill all the cancer cells that had broken off from main tumor and spread to the blood or lymphatic system or any part of the body. This killing process of cells is either by a direct effect on deoxyribonucleic acid (DNA) or an effect on the factors involved in mitosis by inhibition of its synthesis or production or uses [7-9]. Chemotherapy drug may lead to complete cure of some types of cancers or may suppress the growth of others or may prevent their spread to other parts of the body. So types of new therapies have emerged over the past 20 years. Some of them were straight forward, effective, and safe and some have many side effects. However when comparing chemotherapy with other types of treatments, it still remains potentially high risk with many side effects which are difficult to manage. The chemotherapy used required the involvement of various clinical professionals during its various stages of administration and enomorous patient health care is needed to overcome its side effects [7, 10].

Chemotherapy side effect-

The goal of chemotherapy is to be as possible with tolerable side effects, since the dose of chemotherapy will be toxic to the cancer cells as well as to the normal cells.

A proportion of the cancer patients suffer from only mild side effects, whereas others may suffer from serious side effects.

The side effects are classified as:

- Acute, which develop within 24 hours after chemotherapy administration.
- Delayed, which developed after 24 hours and up to 6-8 weeks after chemotherapytreatments.
- Shorts term, combination of both acute and delayed effects.
- Late/ long term, which developed after months or years of chemotherapy treatments.
- Expected, which developed among 75% of the patients.

- Common, occurred in 25-75% of the patients.
- Uncommon, happened less than 15% of the patients.
- Very rare, occur on less than 1% of the patients.

Occurrence of specific side effects will vary according to the chemotherapy used. The most common side effects experienced are nausea and vomiting, anemia, hair lost, bleeding, thrombocytopenia, bone marrow depression, alopecia, and mucositis. So different parameters must be taken into consideration to prevent, reduce, and overcome these side effects [10-12].

Plants and cancer-

Herbal medicine has been used as major treatment for cancer in various countries in the Middle East and Europe long time ago. Recent reports released by the World Health Organization (WHO) showed that although many advanced countries have considered traditional herbal treatment as an official treatment for cancer, only 5-15% of these herbs have been investigated to detect their bioactive compounds, i.e., anticancer compound [13-15].

What is Cancer???

Cancer is one of the major causes of death in world, and it is the second leading cause of mortality after cardiovascular disease [16].

Cancer starts with the deformation of natural cells caused by genetic mutations in DNA. This abnormal way by asexual reproduction that is, it ignores signals related to regulation of cell's growth around it and obtains invasion characteristics and causes changes in surrounded tissues [17].

Every year, an average 182 per 100,000 persons suffer from cancer worilwide, and 102 die by cancer. Accourdig to World Health Organization, 14 million people suffer fromcancer and 8 million die by cancer worldwide [18].

How Cancer occur???

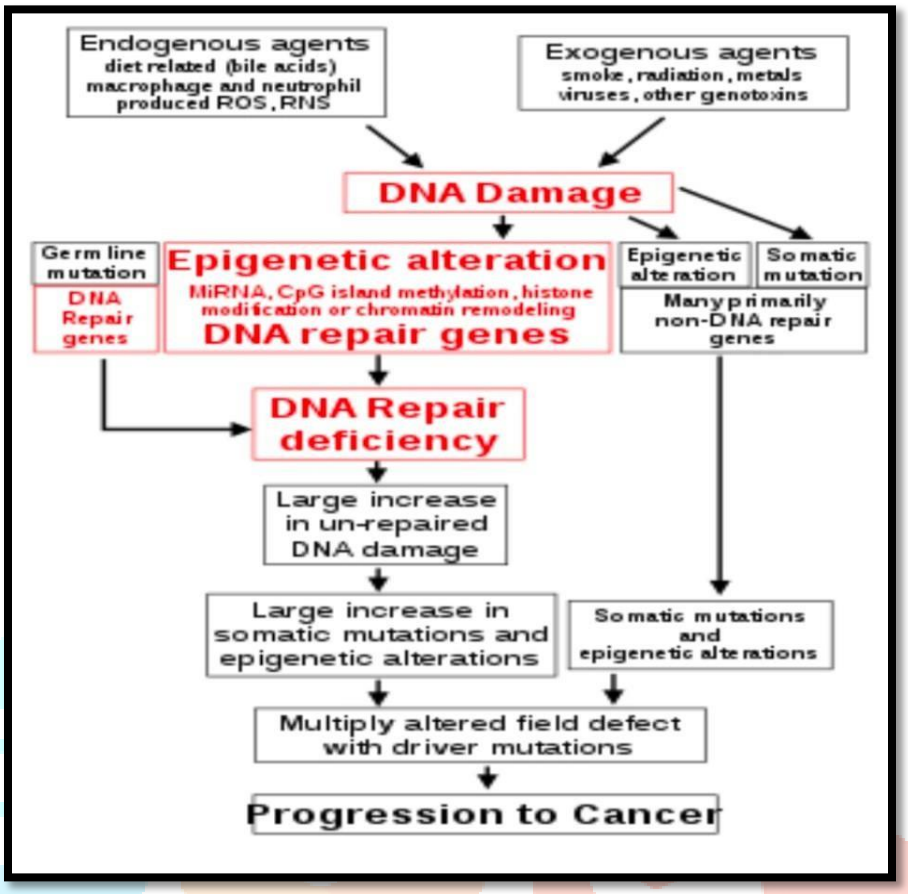

Fig.No 1. Occuring of cancer

Classification of cancer-

Tumors are traditionally classified four ways-i By

tissue, organ, and system

ii Specific type

iii Grade accourding to WHO classification

iv By spread accourding to the Tumor Node Metastatis (TNM) system [19].

ANTI-CANCER ACTIVITY OF MEDICINAL PLANTS

Medicinal plants have various advantages over chemical products, because plantderived compounds are more tolerated and non-toxic to the normal human cells.

Already available conventional therapies for the treatment of cancer are radiotherapy and chemotherapy and they have possesses various side effects like neurological, cardiac, renal and pulmonary toxicity, which seriously affects the health of the person. Therefore, an alternative method is required to develop that include less toxic and more potent anticancer drug as compare to drugs available in market.

1] ANDROGRAPHIS PANICULATA-

Fig.No 2. Andrographis Paniculata

- Synonym- Kalmegha (Hindi)
- Biological source- It is a commonly known as creat or green chiretta, is an annualherbaceous plant, belonging to family *"Acanthaceae"*
- Chemical constituents- andrographolide
- Origin- It is found in India and Sri Lanka.

Generally, roots and leaves are used for the medicinal purpose; extract of this plant contains flavonoids, stigmasterols and diterpenes [20].

The main compound of this plant the andrographolide which is a diterpene, it is colorless crystalline in nature and bitter in taste. Leaves contains highest amount of andrographolide (approximately 2.25%) while the seeds contains very low amount of this compound. Studies in the mice have shown that Andrographis paniculata stimulates immune system and activates both the antigen specific and non specific immune response. Due to thisability, plant is effective against various oncogenic and infectious agent [21].

Andrographolide shows cytotoxic effects against various cancer cells [22]. It shows cytotoxic effects against breast cancer cells, P388lymphocytic cells and colon cancer cells. Andrographolide shows inhibition of growth in colon cancer cell line HT 29 and enhance growth and division of human peripheral blood lymphocytes on mouse myeloid leukemia M1cell lines [23].

2] AZADRIACHTA INDICA-

Fig. No. 3. Azadriachta Indica

- Synonym- Neem, Indian liliac.
- Biological source- It is consists of fresh or dried leaves and seed oil of Azadirachtaindica J.Juss, belonging to family *"Meliacear"*
- Chemical constituents- Limonoidncluding azadirachtin and nimbolide.
- Origin- India

The chemical constituents that induce apoptosis of tumor cells by targeting different cells signaling pathways.

There are various theories of cell apoptosis by neem such as activation of proapoptoticproteins like Bax and Bak to permeabilize mitochondria and inhibiting the activity of Bcl-2 and mutant p53 in the 7, 12-dimethylbenz anthracene (DMBA) induced cancer cells. However there is no evidence on the culminating reasons of neem induced apoptosis. A study on limonoids shows that neem exhibits caspase dependent cell apoptosis and release reactive oxygen species toinhibit metastasis [24].

The neem leaf glycoprotein the activity of M2 macrophages, by converting it to M1 phenotypes in tumor core. This restricts the hrowth of the melanoma and prevents the relapse of tumor by disseminating tumor mass.

The vital properties of neem components on tumor cells include enhancing immune response, inhibition cell proliferation, including cell apoptosis, suppression of cancer angiogenesis, and restoration of cellular reduction/oxidation balance. Neem exteacts enhance efficacy of immunotherapy and radiotherapy.

3] BOSENBERGIA PANDURATA-

Fig.No 4. Bosanbergia Pandurata

- Synonym- Finger root, Chinese ginger.
- Biological source- Bosenbergia pandurata is a ginger species. Belonging to family *"Zingiberaceae"*
- Chemical constituents- Bosenbergin, cardamonin, pinostrobin, pinocembrin,panduratin A, 4-hydroxypanduratin A.
- Origin- Southeast Asia, India, Sri Lanka, Sothern china.

The active compounds act as antioxidant, antibacterial, antifungal anti-inflammatory, antitumor and anti-tuberculosis agents.

A cyclohexenylchalcone derivative, derivative, panduratin A, present in B. pandurate is shown to inhibit the growth and induce apoptosis of HT-29 colon cancer cells line. A study reported that Panduratin A arrested the cancer cell lines A549 non-small cell lung cancer; PC3 and DU145 prostate cancer cells and illustrated proapoptotic activities.

Mohd Isa et al. Investigated the anticancer role of bosengergia a (BA) isolated from Bosenbergia rotunda in human non-small cell lung cancer (A459) cells. BA arrested the cell cycle by accumating the cells in sub G1 phase. BA stimulated the expression of pro-apoptotic Bcl-2 family members, caspase 3/7, 9 and 8. The study thus concludes that BA could be a promising agent for the treatment of lung cancer [25].

4] BOSWELLIA SERRATA-

Fig. No. 5. Boswellia serrata

- Synonym- Olibanum, Indian olibanum.
- Biological source- It is an herbal extract taken from Bosewellia serrata tree.Belonging to family *"Bursersceae".*
- Chemical constituents- It contains various compounds like terpenoids, oils andsugars. The man constitute of this plant is Bosellic acid [26].
- Origin- India, North Africa and Middle East.

Gummy exudates of this plant are associated with the therapeutic effect which includes astringent, stimulant and anti-septic effects. Acetyl-11-keto-b-bosewellic acid which is an active compound of this plant shows potential activity to inhibit tumor angiogenesis through the vascular endothelial growth factor signaling.

Studies showed that treatment with acetyl-11-keto-b-bosewellic acid (dose- 10mg/kg) suppress tumor growth in xenograft mice with human prostate [27]. This shows the anti-tumor activity of this plant.

5] CAPPARIS SPINOSA-

- Synonym- Himsra, cabra in Sanskrit.
- Biological source- Capparis spinosa fruit extract is an extract of the buds and berriesof the caper. Belonging to family *"Capparaceaen".*
- Chemical constituents- Caper constitutes various volatile and non-volatile compoundslike flavonol glycoside, rutinand 5-caffeoyl-quinic acid.
- Origin- Mediterranean and Middle Eastern cuisines.

Rutinand 5-caffeoyl-quinic acid those are potent anti-cancer agent. A protein analogus to imidazoleglycerol phosphate synthase was purified from fresh caper seeds, that inhibited proliferation of hepatoma HepG2 cells, colon cancer HT29 cells and breast cancer MCF-7 cells [28].

Fig. No. 6. Cpparis Spinosa

Essential oils and aqueous infusions extracted from caper have shown significant inhibitory effect on HT-29 cell proliferation and on nuclear factor kB (NF-kB) activity in a dose dependent manner. Caper essential oil and aqueous infusion ceased the cells in G2/ M phase of cell cycle. A study has reported C.spinosa extract mediated apoptosis through permeabliztion of mitochondria and activation of Caspase 9 in SGC-7901 cells [29]

6] CENTELLA ASIATICA-

- Synonym- Brahmamanduki (Hindi), mandukaparni (Sanskrit), pennywort (English)
- Biological Source- Centella Asiatica is a tropical medicinal plant Belonging tofamily *"Apiaceae"*
- Chemical constituents- It contains numerous compounds such as asiaticoside, pecticacid, hydrocotyline, sterol, flavonoid, vallerine, ascorbic acid and thankunosides [30].
- Origin- It is commonly found in India, Australia, Pacific Island, New Guinea, Iranand Malaysia.

Partially purified fraction of centella asiatica suppressed mouse lung fibroblast cell proliferation and oral administration slowed the solid development and ascites tumours [31]. Pre-treatment with this plant increase the survival time of irradiated animals and show protection against radiation induces damage in liver [32].

This plant shows inhibition in lipid peroxidation in various organs like lungs, liver, heart, brain, spleen and kidney and shows potential towards the cancer inhibition [33].

Fig. No. 7 Centella Asiatica

7] CURCUMA LONGA-

- Synonym- haldi (Hindi), harida (Sanskrit), turmeric (English)
- Biological source- Curcumin is the active ingredient of dietary spice turmeric and isextracted from the rhizomes of C. longa Belonging to family *"Zingiberaceae"*
- Chemical constituents- Curcumin is a active ingredient in this plant.
- Origin- South or Southeast Asia, Vietnam, China or Western India.

Curcumin is a active ingredient polyphenol derived from plant rhizome and this plant is used for both cancer prevention and treatment. Numerous studies showed that curcumin induces apoptosis, interfere with progression of cell cycle and inhibits proliferation [34].

Curcumin also showed colon and gastric cancer prevention in rodents [35].

Fig. No. 8 Curcuma longa

Curcumin shows protective effect by inhibiting growth of several angiogenesis associates and

tumor associated genes [36]. Curcumin shows anticancer activity by inhibiting theproliferation of tumor cells.

Curcumin possess anti-proliferative property by down regulating the numerous gene expression which includes activator protein 1, NF- kappa B, cycloxygenase 2, epidermal growth receptor 1, nitric oxidase synthase and tumor necrosis factor [37].

8] PANAX GINSENG-

- Synonym- Asian ginseng, Chinese ginseng, Korean ginseng.
- Biological source- It is a species of plant whose root is the most original source ofginseng. Belonging to family *"Araliaceae".*
- Chemical constituents- Active compound is ginsesosides which is steroidal saponin.
- Origin- Korea, China, Japan, United States and Russia [38]

Fig. No. 9 Panax ginseng

It possess anti-inflammatory and immune-modulatory activity and also helps in the appetite stimulation, physical stamina improvement, memory enhancement ad behavior [39]. Anti-cancer activity of ginsenosides is due to the induction of cell death and its other properties as an anti-invasion, anti-angiogenesis and anti-proliferation activity [40].

9] PSIDIUM CATTLEIANUM-

Fig. No. 10 Psidium Cattleianum

- Synonym- Strawberry guava, cattle guava.
- Biological source- It is a small tree in the myrtle Belonging to family "*Myrtaceeae"*
- Chemical constituents- More than 200 volatile compounds have been identified in thefruit oil p.cattleiaunm.
- Origin- Brazil.

In a study conducted by moon et al 2011, the anticancer properties of chloroform extract of p.cattleianum leaves were reported. The effect of chloroform fraction of guava leaf extract was evaluated against various cancer cell line. Significant cytotoxicity was observed against SNU-16, a gastric cancer cell line. Strawberry guava acts as an inducer of apoptosis and inhibits the proliferation of cancer cells.

It induces apoptosis by stimulating the activities of proapoptopic factors like caspase-8, caspase-3 Bcl-2. Bax and poly (ADP-ribose) polymerase (PARP). The chloroform extract of guava leaves ceases the SNU-16 cancer cell lines in G1 phase of the cell cycle thus acting as an anti-proleferative agent.

10] PHYLLANTHUS AMARUS-

- Synonym- Jaramla (Hindi), bhumymalaki (Sanskrit), stone breaker (English)
- Biological source- It is a Indian phyllanthus amarus deciduous tree. Belonging tofamily *"Euphorbiaceae".*
- Chemical constituents- It P. amarus contains flavanoids, tannins and lignans.
- Origin- Asia (warmer parts of India)

Fig No. 11 Phyllanthus amarus.

Whole plant, shots, roots and leaves are utilized for the medicinal purpose. Flavanoids, tannins and lignans which present in p. amarus which are used for the liver, stomach, kidney, spleen and genitourinary system problems.

Oral administration of p. amarus extract reduce tumor size and increase life span in mice bearing Erlich ascites carcinoma and Dalton's lymphoma ascites. Anticancer activities of this plant are due to the ability to induce cell cycle arrest, interfere with DNA repair and inhibition of metabolic activation of carcinogenic compounds [41]. Extract of p.amarus also showed anti-angiogenic effects in mice (bearing Lewis lung carcinoma) by interfering with the vascular endothelial cells migration.[42]

11] PLUMBAGO ZEYLANICA-

Fig No. 12 Plumbago Zeylancia

- Synonym- White leadwort, chitrak, Ceylon leadwort.
- Biological source- It is plant species Plumbago Zelyancia is a distributed as a weed throughout the tropical and subtropical countries. Belonging to family "*plumbaginaceae"*
- Chemical constituents- Presence of various phytocompounds which includes plumbagin, plumbagin acid, coumarins, saponaretin, isoaffinetin, isoorientin, steroids, glucosides and psoralen [43].
- Origin- Warmer part of India and Sri Lanka.

This plant shows therapeutic activity against skin diseases, rheumatic pain, wounds and scabies [44].

Plumbagin is a napthoquinone which is isolate from the roots of this plant and it possess anti-tumor activity by controlling the hormone refractory invasive prostate cancer. Inhibitory effect of plunbagin against various molecular targets (STAT-3, AKT and PI-3K). results in the growth inhibition and invasion of prostate cancer. Plumbagin shows apoptosis induction in cancer cells and also inhibits growth of these cells.

12] RHINACANTHUS NASUTUS-

Fig No. 13 Rhinacanthus Nasutus

- Synonym- Snake Jasmine.
- Biological source- It is a medical herb found in sub-conterental parts Belonging tofamily "*Acanthaceae"*
- Chemical constituents- It contains rhinacathins (A-D,G-Q), napthoquinone, ligningroups and rhinacanthone [45].
- Origin- India, China and Southeast Asia.

This plant shows potential in the treatment of pulmonary tuberculosis, eczema, diabetes and herps, Studies showed that rhinacanthins M, N and Q inhibits human cancer cell (HeLa, HepG2 and KB) growth and normal Vero cells. Rhinacanthins N partially arrest the M phase cells and prevents from further damage and repair cell defects [46].

13] SCUTELLARIA BAICALENSIS-

Fig No. 14 Scutellaria Baicalenesis

- Synonym- Baikal, scute, scutellaria.
- Biological source- It is a georgi species of flowering plant Belonging to family"*Lamiaceae"*
- Chemical constituents- It contains chalcones, anthocyanidins, flavanones, flavonols,flavanonols, and flavones.
- Origin- Eastern Asia.

Its anti-tumor property is due to the presence of wogonosid, wogonin, baicalein and skullcapflavone II. All these compounds (at micro molar concentrations) show inhibitory effects against hyman tumor cell lines 529L and LXFL proliferation.

Baicalein inhibits the activity of 12-lipooxygenase and contributes to the anti-cancer activity against various other cancers [47]. It also possesses anti-inflammatory, anti-diabetic, anti-tumor, hepatoprotective, anti-anxiety and anti-hypertensive effect [48].

14] TINOSPORA CORDIFOLIA-

- Synonym- Giloya, Guduchi, heartleaf moonseed.
- Biological source- It is a herbaceous vine Belonging to family "*Menispermaceae"*
- Chemical constituents- Root of this plant contains various alkaloids which includes tinosporin, choline, isocolumbin, columbin, tetrahydroplamatine, mangoflorimne and palmatin [49].
- Origin- Sri Lanka, India, Myanmar, China.

Fig. No 15 Tinospra Cordiofolia

Tinospora cardiofolia stem is generally used for the treatment of fever, dyspepsia, jaundice, skin and urinary diseases [50].

In-vitro study shows tinospora cardiofolia able to kill HeLa cells this shows the potential of this plant as an anticancer agent. Tinospora cardiofolia extract shows dose dependentcell death as compared to the controls [51]. Dichloromethane extract of T.cardiofolia showed anticancer activity in mice transplanted with Ehrlich ascites carcinoma [52].

15] VITIS VINIERA-

- Synonym- Grape vine.
- Biological source- The grape is eaten fresh, processed to make wine, vinegar or juice,or dried to produce resins. Belonging to family "*Vitaceae"*
- Chemical constituents- Organic acids, phenolic acids, lipid, enzymes, carotenoids,terpenes, and reducing and non-reducing sugars.
- Origin- Southwestern Asia

Fig No. 16 Vitis Vinifera

Grape extracts exhibit cytotoxic effect against PC-3, A-549 and MCF-7 cancer cells. Extracts isolated from the grape seeds and stems demonstrated antitumor activity in human breast cancer cell lines MCF-7 and MDA-MB-23, colon (HT29), renal (786-0 and Caki-1), thyroid (K1), hepatocellular carcinoma cell lines, oral squamous cell carcinoma and normal human fibroblasts [53].

Grape skin possesses a chemopreventive agent, Resveratrol that induces autophagy and acts as an anticancer agent. In a clinical trial methanolic extracts from Greek raisins have been reported to demonstrate a decrease in gastric cancer cell proliferation and mRNA levels of ICAM-1 in TNF-alpha stimulated cells with an induction in cell apoptosis and inhibition of inflammation [54].

16] XANTHIUM STRUMARIUM-

- Synonym- burweed, cocklebur.
- Biological source- It is a common annual weed spread by water, humans or other animals. Belonging to family *"Asteraceae".*
- Chemical constituents- It contains xanthinin, xanthumin, xanthostrumarin, xanthatin, phytosterols, xanthanolides, isoxanthonol, xanthanol and xanthinosin. 8-epi-xanthin and its epoxide.
- Origin- North America.

Fig. No. 17. Xanthium strumarium

It possesses anti-bacterial, anti-fungal, anti-tumor, anti-tussive-, anti-inflammatory, anti-micotic, anti-malarial, anti-oxidant, analgesic and insecticidal activities. 8-epi-xanthatin and its epoxide shows anti-tumor activity by inhibiting the tumor cell lines proliferation. 8-epi- xanthatin acts as a farnesyl transferse inhibitor and also inhibits microtubules interfering agents, this shows the potential of 8-epi-xanthatin in the anti-cancer activity [55].

17] ZIZIPHUS NUMMULARIA-

Fig No 18 Ziziphus Nummularia

- Synonym- Harbor, bhukamtaka sukhsharanphala, wild jujube.
- Biological source- It is a tropical fruit tree species Belonging to family"*Rhamnaceae".*
- Chemical constituents- Betulinic acid, betulin.
- Origin- Iran, India, Iraq, Israel, Pakistan, Afghanistan.

Stem, bark, roots, seeds and flowers of this plant used for the medicinal purpose. Betulic acid and betulinic are the active constitutes of this plant which shows anti-tumor activity. Betulnic acid shows

cytotoxicity against various tumor cell lines and induces apoptosis by topoisomerase I inhibition, reactive oxygen species generation, angiogenesis inhibition and pro- growth transcriptional activator modulation. Betulinic acid also induces apoptosis by CD 95 and p53 independent mechanism, these mechanisms shows the potential of this compound against thecancer cells [56-67]

Conclusion-

Extracts of various medicinal plants and their secondary metabolites are responsible for the anti-cancer activity. This review contains medicinal plants with their secondary metabolites activity. That show anti-cancer *In-vitro* studies have showed the potential secondary metabolites in the anti-cancer activity and plant metabolites mentioned in this review possesses variety of mechanisms that contributes to their anti-cancer nature.

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