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Crude Drugs Using as Anticancer Agents

Bhaskar G*, Gopinath E, Vineeth Chandy

Department of Pharmacy, T John college of Pharmacy, Bangalore, Karnataka, India

Abstract

There is a more progress has been made in the development of novel cancer treatments. But the cancer remained as a leading cause death in the world. The etiopathognesis of cancer is due to the because of genetic predisposition, and also there is some environmental factors associated with cancer are some of them are may be due to environmental toxins, and also life style and diet if the cancer is relapsed also there is a chances of high risk of death rates due to the toxicity of drugs. In current scenario the therapy for cancer is followed by Surgery Chemotherapy, radiotherapy, etc. through all this by current therapy we can't cure cancer completely. The particularly chemotherapy is the most commonly used treatment to treat the cancer but this chemotherapy associated with more adverse effects which leads to severe. So the main purpose of brief review is to understand the current uses of crude drugs as an anticancer to have a better result of the drug targets in the cancer therapy as anticancer. But pharmacological role of these crude drugs in cancer therapy is not fully clear. But many researchers are in believed that these crude drugs are to have nutraceutical effects on cancer patients.

Keywords: Crude drug • Cancer • Cell inflammation • apoptosis • Environmental toxins • Nutraceutical

Introduction

Cancer is the uncontrolled cell growth and abnormal proliferation of cell division and this cancer is the one of the leading cause of death and this cancer is the one of the causes for morbidity and as well as mortality [1]. So as to treat this cancer condition we have to go for anticancer therapy by using anticancer agents. This anticancer agent plays a role in targeted cell destruction this is called as apoptosis. This apoptosis is defined as a programmed cell death. But the use of anticancer agents will also affect the healthy cells which are surrounded by the cancer cells [2]. So in order to limit the side effects on healthy cells we are trying to use crude drugs as an anticancer.

We all know that the history of medicine, in earlier period that the so many effective drugs were derived mainly from the extracts of plants and animals. We have a aware that the cinchona bark is used as an antimalarial they extracted the quinine drug from the cinchona bark this was an small example of the drug to extract from the crude drug. So in thought of this many researchers were decided to discover anticancer drugs from the crude drugs from the nature.

The drugs come from naturally by the form of plants source is called as crude drugs. This crude drug is used as a Pro-drug [3] .Some of the natural substances such as metabolites extracted from the plants using different mechanisms to induce apoptosis in cancer cells which are blocked. Some combinations of plant extracts such as vinca alkaloid compounds, podophyllotoxin and Camptothecin in cancer treatment have been used. There are number of plant resources are available on our earth but the only few of them have been used in cancer treatment in the clinical trials [4]. But at present also most importance will be given for chemotherapy, Radiation therapy, or Surgery this will used as treatment for cancer. This all could be successful but it has some drawbacks also. Like Chemotherapy has a severe side effects on healthy cells and that healthy cells get damage [5].

This crude drugs used as pro-drug in anticancer on their effectiveness this can directly administered or else as supplemental in the clinical trials (Tables 1 and 2).

***Address for Correspondence:** Bhaskar G, Department of Pharmacy, T John college of Pharmacy, Bangalore, Karnataka, India, Tel: 9113016597; E-mail: bhaskargangadhar765@gmail.com*

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Paclitaxel

Paclitaxel (Taxol), it is a crude drug approved for treating a variety of cancers. It is a crude drug obtained from the bark of the slow growing and endangered Pacific yew-Taxus brevifolia from the tree family Taxacae, Paclitaxel has an organic chemical terpenoid it was first extracted from the yew tree in the US in 1971 and recieved an approval from the US Food and Drug Administration for clincal use in 1992. Paclitaxel has proved effective treatment in many types of cancers, such as ovarian cancer, breast, Lung, Esophageal and liver cancers [6]. The mechanism action of paclitaxel are that it binds to β - tubulin in the micro-tubule specifically and reversible inhibits cell division, blocks cell mitosis, stabilizes cytoplasmic micro-tubules, and induces the formation of the characteristics microtubule bundles in cells [7].

Curcumin

Curcumin is an natural compound obtained from the plant Curcuma longa it is used in the Indian traditional food as the yellow coloring agent in turmeric, is known for its antioxidant, anti-inflammatory, anti-viral, antibacterial, antifungal,

Table 1: Plant drugs influenced in cancer treatment.

Sl.No	Metabolites	Extracted drugs
1	Vinca	Vincristine
2	Vinca	Vinblastine
3	Vinca	Vindesine
4	Vinca	Vincrelbine
5	Taxan	Paclitaxel
6	Taxan	Docetaxel
7	Podophyllotoxin	Topotecan
8	Podophhyllotoxin	Irinotechan
9	Anthracyclines	Doxorubicin
10	Anthracyclines	Daunorubicin
11	Anthracyclines	Epirubicin
12	Anthracyclines	Idarubicin

Table 2: Extracted metabolites influence in different cancers.

Sl.no	Metabolites	Groups	Plant species	Type of cancer
1	Cucumin	Phenolic	Curcuma	Colorectal cancer
2	Resveraterol	Phytoalexin	Grapes	Breast cancer
3	Genistein	Flavonoides	Soya beans	Leukemia
4	Biocalein	Flavonoides	Shosiko	Hepatocellular
5	Hydroxystaurosporin	Alkaloid	Viscom album	Ovarian cancer
6	Lectine	Lectines	Many plants	ALL
7	Xanthorrhizol	Terpenoids	Curcuma	Cervical cancer

and anticancer activities [8].In studies of Curcumin shows that to interact with a wide variety of proteins and modify their expression and activity. This protein includes inflammatory cytokines and enzymes, transcription factors, and gene products, invasion, and angiogenesis [9]. Several clinical trials have indicated the curcumin is safe and may exhibit therapeutic efficacy. Recent studies of Curcumin has reported that Curcumin decreased survival of RT4V6 and KU7 bladder cancer cells in part at least through increased DNA fragmentation and other parameters associated with apoptosis [10].The Curcumin alone had minimal effects on NF-κB activation when the activation was induced by agents, such as gemcitabine, tumor necrosis factor-alpha (TNF-α), The investigators has concluded that suppression of induced NF-κB by curcumin may play a role in sensitizing bladder cancer cells and other cancer cell lines to various chemotherapeutic agents [11].

Carotenoids

Carotenoids are also found in colored fruits and vegetables or sea food; these carotenoids have strong cancer-fighting properties. These carotenoids have the anticancer effect due to their antioxidant properties. These antioxidants protect cells from free radicals, substances that work to destroy cell membranes and DNA. These Carotenoids may help to prevent prostate, breast and skin cancer as well as endometrial cancer [12].

Astaxanthin is another carotenoid, found in salmon, red fish, shrimp and crab, which shows anti-carcinogenic effects shown in mouse lung and liver cancer models. In the HepG2 human liver cancer cell line, astaxanthin significantly inhibited, in a dose-dependent manner, the proliferation of liver cells. The astaxanthin restrained the cell cycle progression at G1 and induced apoptosis. The astaxanthin will be a better agent for use in chemoprevention or as a cancer therapeutic [13].

Resveratrol

Resveratrol is a crude drug found in the skin of red grapes and also in red wine that has been identified on the basis of its ability to inhibit cyclooxygenase (COX) activity is resveratrol. Resveratrol inhibits cellular events associated with tumor initiation, promotion, and progression. It suppresses TNF-α-induced activation of nuclear transcription factors NF-κB, activator protein-1 (AP-1) and apoptosis, suggesting a potential role in reducing oxidative stress and lipid peroxidation [14].

Herbals

Scutellaria balcalensis with the common name Baikal skullcap or chinese skull cap is a widely used chinese herbal medicine previously this medicines are used as an anti-inflammatory and as well as anticancer therapy this has been tested as a treatment for prostate cancer. Two human prostate cancer cell lines (LNCap, androgen dependent and PC-3, androgen independent) were assessed for growth inhibition when exposed to *Scutellaria balcalensis*. This *Scutellaria balcalensis* exerted dose dependent and also time dependent increased growth inhibition in both cell lines. After the treatment with *Scutellaria balcalensis*, PGE2 synthesis in both cells was significantly reduced, resulting from direct inhibition of COX-2 activity rather than COX-2 protein suppression. *Scutellaria balcalensis* also inhibited prostate specific antigen production in LNCap cells. As finally the Scutellaria balcalensis suppressed expression of cyclin D1 in LNCap cells, resulting in a G1 phase arrest, while inhibiting cdk1 expression and kinase activity in PC-3 cells, ultimately leading to a G2/M cell cycle arrest. The studies on animal showed that after a 7-week of treatment period with Scutellaria balcalensis we have reported as tumor volume was reduced by 50%, so this has been demonstrated has that Scutellaria balcalensis may be a novel anticancer agent for treating in prostate cancer Table 3 [15].

Vinca alkaloids

Vinca alkaloids are a versatile group of plant chemicals isolated *from Catharanthus roseus* (*C.roseus*) belongs to the family *apocynaceae* and are used as the therapy for several type of cancer namely, Breast cancer, Liver cancer, Leukemia, Testes cancer, lung cancer. The four main vinca alkaloids in use are: Vinorelbine, Vindesine, Vincristine, and Vinblastine [16]. The vinca alkaloids (*Vincristine* and *Vinblastine*) bind to a specific site termed as tubulin heterodimers (vinca-binding site) disrupting the functions of microtubules or by arresting cell cycle at metaphase [17]. Currently semi synthetic derivatives of vinca alkaloids are vinorelbine, vindesine, vinfosiltine and vinovelbine which have been introduced in the market. These derivatives are used alone or in combination with other phytochemicals agents to fight against large number of cancer [18].

Campothecin derivatives

Campothecin this are first isolated from the Camptotheca acuminata belongs to the family *Nyssaceae* this are having the (family of *topoisomerase* I poisons) [19]. The active constituents which have shown efficacy which has been isolated that has been identified as camptothecin. This camptothecin derivatives like topotecan (hycamtin) and irinotecan, where irinotecan is used to treat colorectal cancer while topotecan is used to treat ovarian and lung cancer [20].

Capsaicin

Capsaicin is also a natural plant chemicals isolated from red pepper and exert strong anticancer, antimutagenic, anti-metastatic, anti-angiogenic and chemo preventive functions in pancreatic, prostatic, liver, skin, leukemia, lung, bladder, colon, and endothelial cells [21]. Capsaicin regulate different molecular targets in brest cancer like, caspase-3, reactive oxygen species (ROS), Rac1, and HER-2 [22]. Capsaicin is more potent by including apoptosis in the presence of p53 gene product. Capsaicin produced apoptosis in breast cancer (H-Ras, MCF10A cells) by inducing ROS and Rac1 signaling pathways. These ROS and Rac1 pathways are specifically induced by proteins like, p38, c-jun N-terminal protein kinase-1 [23].

Combretastatin

Combretastatin is a stilbene derivative this is present in the Combretum caffrium tree, also known as the "African willow", which grows in the southeastern region of Africa. The stilbene derivative, it may exist in Trans (combretastatin A-1 (CA-1) and cis (combretastatin A-4 (CA-4). Combretastatin A-4 and its derivatives were synthesized by petti and his collegues in 1987 [24]. The new synthesis of new derivatives of podophylotoxins was performed and these were tested on skin carcinoma, human cervix adenocarcinoma HeLa, breast cancer cell lines: MCF7, MDA-MB-231, lung carcinoma and ovarian cancer cells SKOV. These compounds inhibit tubulin polymerization with IC50 values below 1μM [25]. Combretastatin are microtubule -targeting drugs similar to taxanes and vinca alkaloids. These compounds belong to the class of vascular disrupting agents, which inhibit the angiogenesis of the tumor blood vessels. The mechanism of action of combretastain as an antineoplastic compound is an associated with its binding to β-tubulin at which is known as the colchicine site, causing the destabilisation of the microtubules. Inhibition of the tubulin polymerization prevents the cancer cells from producing microtubules, which leads to the inhibition of cell proliferation, resulting in the process apoptosis [26].

Podophyllotoxin

Podophyllotoxin is a toxin lignan isolated from the *Berberidaceae* family (i.e; *podophyllum*). The resin known as podopyllin was obtained from the

Table 3: Crude drugs or elements of crude drugs at target site showing as anticancer property.

Crude drugs	Targets
Paclitaxel (Taxol)	β - tubulin
Curcumin	Multiple targets
Astaxanthin	P21CIP/WAF,GADD153,c-myc
Citrus pectin	NF - κB
Mushroom	CD4, CD8, CD25, IFN - γ, IL-6, TNF - α
Resveratrol	NF - κB
EGCG (epigallocatechin -3-gallate)	VEGF,NF -κB, IKKβ, IκB - α
Scutellaria baicalensis	COX - 2, Cyclin D1
Artemisia asiatica	P38, NF - κB
Red ginseng	CD-1
Isoliquiritigenin	P21CIP/WAF
Capsaicin	Bcl-2

podophyllum peltatum species found in north America. Podophyllotoxin was extracted from *Podophyllum* emodi resin from asia[27].

Podophyllotoxin also occurs in the plants of the *Linum* and *Juniperus* species and in *Podophyllum versipelle* [28]. *Podophyllum* peltatum plants also contain α-peltatin,β-peltatin and their corresponding glycosides, along with podophyllotoxin-α-D-glucoside. The first synthesis of podophyllotoxin was performed by Gensler and Gatsonis in 1962. Podophyllotoxin and its derivatives are aryl tetralin lactone compounds that contain the lactone ring in its trans conformation. Podophyllotoxin and its derivatives exhibit significant biological activity as antiviral agents and antineoplastic drugs. Podophyllotoxin and its glycosides exhibit a very strong cytostatic effect, as they disrupt the karyokinetic spindle. These compounds attach to the colchicine domain of tubulin and inhibit tubulin polymerisation. In DNA through their interactions with DNA topoisomerase II, inducing cell-cycle arrest in the G2-phase of the cell cycle. This activity is mediated through the formation of a stable complex with DNA and topoisomerase II.Etoposide and teniposide are the semisynthetic derivatives of podophyllotoxin and exhibit cytostatic activity.

In primary brain tumour cases, including paediatric patients with relapsed brain tumors, as a salvage treatment. The majority of the patients receive etoposide as a part of a multi-agent regimen that includes cisplatin, carboplatin, cyclophosphamide, Vincristine,and etoposide [29,30]. Etoposide and teniposide stabilise the intermediate covalent complexes formed between topoisomerase II and the cleaved DNA as well as the induction of DNA damage, which arrests the cell cycle in metaphase and leads to apoptotic processes [31,32]. Podophyllotoxin is also used for the semisynthesis of anticancer drugs such as etoposide, teniopside, azatoxin, and etopophos as well as NK611, GL331, TOP-53, and Tafluposide [32,33]. Podophyllotoxin derivatives are used in the treatment of numerous cancers, such as lymphomas, neuroblastomas, sarcomas, testicular carcinoma and ovarian cancers, colon cancers, breast cancer, prostate cancer, small-cell lung cancer [34]. podophyllotoxin is a highly toxic compound, and therefore, it is rarely used in cancer therapy [35].

Conclusions

Modern chemotherapy utilises many substances of plants and aquatic origin. These compounds have cytotoxic properties with many different mechanism of action, such as the inhibition of tumour cell growth, the induction of apoptosis, DNA damage, the induction of topoisomerase I and II. It has been evident from the present review that phytochemicals serve as effective research area with bright future. The growing incidence of cancer and high cost various limitations of the conventional therapy including high cost and high toxicity of present anticancer drugs has faced a severe challenge to all the researchers to design and develop an alternative, eco - friendly, biocompatible and cost-effective strategy in a greener way. High biodegradability and biocompatibility have increased the efficacy of these plant constituents in cancer therapy. This review paper provides information on medicinal plants and their bioactive compounds with potential to cure different types of cancer. But in case of curcumin and epigallocatechin should has been further researched in clinical trials. furthermore extensive research work should be carried out on this plants chemical constituents to evaluate their possible applications, toxicological and particular genotoxic profile against a wide range of cancer in both either in-vitro or in-vivo.

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