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Review Article

ANTICANCER AND ANTIOXIDANT ACTIVITY OF *CROTON*: A REVIEW

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ABSTRACT

Cancer is a biomedically complex group of diseases involving cell transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis. The developing knowledge of cancer biology suggests that administering cytotoxic drug therapy at very high doses is not always appropriate.An alternative approach is to administer lower doses of synergestic organic chemicals which already exist in myriad botanicals. A potential advantage of phytochemicals and other compounds derived from natural products is that they may act through multiple cell-signaling pathways and reduce the development of resistance by cancer cells. New drugs with milder side effects are needed desperately to replace and improve existing medicine and to provide new avenues for treating cancer that resist treatment with current drugs. A great deal of information is now available showing that several natural products are endowed with potent anticancer activity. It has been seen that most natural products with anticancer activity act as strong antioxidants and/or modify the activity of one or more protein kinases involved in cell cycle control. This review focuses on the anticancer and antioxidant activity of *Croton*, one of the largest genera of flowering plants.

Keywords: Anticancer activity, Antioxidant activity, *Croton*

INTRODUCTION

Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumors and neoplasms.One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries and which can then invade adjoining parts of the body and spread to other organs.This process is referred to as metastasis,which is the major cause of death from cancer. Cancer is responsible for many deaths (1in 8) worldwide. The international cancer burden doubled between 1975 and 2000 and is set to double again by 2020 and nearly triple by 2030. There were around 12 million new cancer cases and 7 million cancer deaths worldwide in 2008,with 20-26 million new cases and 13-17 million deaths projected for 2030 [1]. Therefore, the need for an effective management, treatment and cure of cancer is undoubtedly crucial. The control of cancer,one of the leading cause of death worldwide, may benefit from the potential that resides in alternative therapies. Conventional therapies cause serious side effects and, at best, merely extend the patient's lifespan by a few years. Better cancer treatments with milder side effects are desperately needed. There is thus the need to utilise alternative concepts or approaches to the prevention of cancer [2]. An integrative approach for managing a patient with cancer should target the multiple biochemical and physiological pathways that support tumour development and minimize normal-tissue toxicity. Interestingly, both laboratory experiments and clinical trials have demonstrated that when combined with chemotherapy, herbal medicines could raise the efficacy level and lower toxic reactions. These facts raised the feasibility of the combination of herbal medicine and chemotherapy [3]. Higher plants have made important contributions in the area of cancer therapy. Early example includes antileukaemic alkaloids, vinblatine and vincristine, which were both obtained from the Madagascan periwinkle (*Catharanthus roseus* syn. *Vinca roseus*). Other cancer therapeutic agents include taxol, homoharringtonine and several derivatives of camplothein [4].Cancer is a disease that is often characterized by too little apoptosis. Apoptosis or programmed cell death,is a normal component of the development and health of multicellular organisms.Cells die in response to a variety of stimuli and during apoptosis they do so in a controlled regulated fashion. Under normal circumstances damaged cells will undergo apoptosis, but in the case of cancer cells mutations may have occurred that prevent cells from undergoing apoptosis.In these cases there is no check on the cellular proliferation and consequently the disease can progress to the formation of tumors.In many cases these tumors can be difficult to kill as many cancer treatments rely on damaging the cells with radiation or chemicals and mutation in the apoptotic pathway often produce cells that are resistant to this type of attack [5]. Apoptosis can be induced in cells under in vitro conditions by a number of ways.One of the classical systems is exposure of thymocytes to glucocorticoids.Other methodologies include DNA damage either by irradiation,exposure to drugs that inhibit topoisomerase, withdrawal of growth factors from growth media, cell cycle perturbation, exposure to inhibitors/activators of kinases or phosphatases, interference with Ca^{2+} homeostasis, overexpression of p**[53]**,members of Ced-3/ICE and many more [6].

Cancers are caused by a number of genetic alterations. Mutation in oncogenes or tumor suppressor genes represent the primary genetic lesions-their activation and inactivation, respectively, trigger carcinogenesis. A large number of mutational events and altered programme of gene expression however,set in when primary tumors evolve to their final malignant state [7].When devastating diseases such as cancer strike, alternative therapies are often sought which employ less toxic and unpleasant treatments than current chemotherapy and radiation treatments [8]. A great deal of information is now available showing that several natural products are endowed with potent anticancer activity. It is indeed difficult to imagine the possible biochemical mechanism of the anticancer action of natural products. Many researchers have recently tested the activity of such products and the possible mechanism of their anticancer action [9-14]. A common activity noted for most of such products is that they act as potent antioxidants and free radical scavengers [8]. Plants are susceptible to damage caused by active oxygen and thus develop numerous antioxidant defence system resulting in formation of numerous potent antioxidants.In simple words "Antioxidants are a type of complex compounds found in our diet that act as a protective shield for our body against certain disastrous enemies(diseases) such as arterial and cardiac diseases, arthritis, cataracts and also premature ageing along with several chronic diseases." Plants contain certain chemicals such as carotenoids, flavonoids, biflavonoids, phenols, phytosterols etc that possess antioxidative properties. Since reactive oxygen radicals play an important role in carcinogenesis and other human disease states, antioxidants present in plants have received considerable attention as cancer chemopreventive agents [15] . The strongest anticancer action has been demonstrated by natural compounds with multifunctional activity. For instance, antioxidants, which also binds to and modulate the activity of protein kinases involved in signal transduction cascades show both cytostatic and cytotoxic activity towards cancer cells.Other activities such as angiogenesis inhibition, nitric oxide synthase inhibition and pro-oxidants production have also been observed [8].

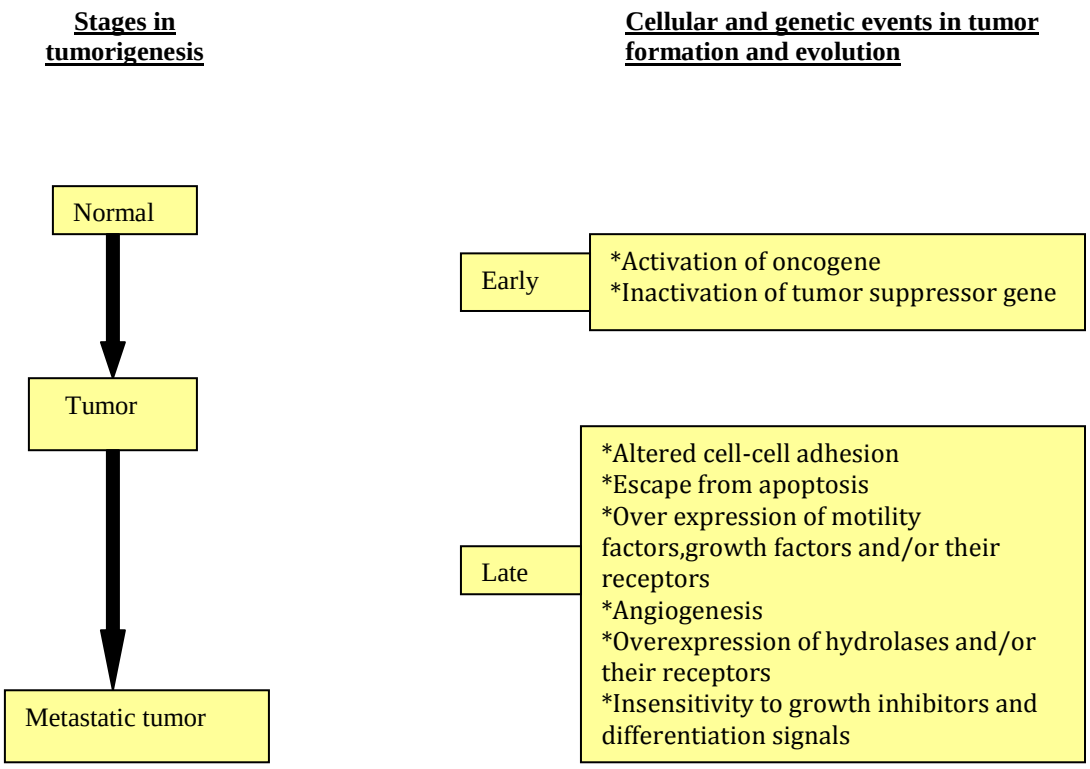


Fig. 1: Stages in tumorigenesis with cellular and genetic events involved in tumor formation and evolution[6].

Croton is an extensive plant genus of the family Euphorbiaceae established by Carolus Linnaeus in 1737 [16]. The flowering plant family Euphorbiaceae,includes 313 genera and over 8100 species that are cosmopolitan in distribution. *Croton* is a "giant genus," with 1223 species accepted in The World Checklist and Bibliography of Euphorbiaceae.But others put the number of species under *Croton* at 1797 starting with *Croton abaitensis* (1st species) and ending in *Croton zeylanicus* (1797th species) [17]. The common names for the genus are rusffoil and croton.The genus name comes from the Greek word "Kroton",which means ticks, because of the seeds resemblance to ticks [16].All the species under *Croton* are herbs, shrubs, trees and occasionally lianas (climbers) that are ecologically prominent and important elements of secondary vegetation in the tropics and subtropics worldwide. From India more than 30 species of *Croton* have been reported so far out of which only six species of *Croton* are used in ethnomedicine. The species are *Croton bonplandianus* Bail., *Croton caudatus* Geisel., *Croton chlorocalyx* Linn., *Croton joufra* Roxb., *Croton roxburghii* Balakr. and *Croton tiglium* Linn. These species are used in the treatment of various diseases, disorders and ailments like antifertility, boils, bowel complaints, chicken pox, cholera, cold and coughs, constipation, cuts and wounds, diarrhoea, dysentry, eye diseases, epilepsy, fever, gastric disorders, insanity, jaundice, liver complaints, malaria, rheumatism, ringworms, scurvy, spasmolytic agent, snake bite, sprains, etc. Recently the use of the powdered roots of *Croton roxburghii* Balakr (known as Hongkai in Arunachal Pradesh), in the treatment of cancer by the Khamti tribe of Arunachal Pradesh have been briefly reported. Also the use of *Croton caudatus* Geisel in the treatment of cancer in the Saikot area of Manipur has been recently reported [17].

Phytochemicals present in *Croton*

Phytochemicals present in the genus *Croton* are considerably diverse. Terpenoids are the predominant secondary metabolite constituents in the genus, chiefly diterpenoids, which may belong to the cembranoid, clerodane, neoclerodane, halimane, isopimarane, kaurane, secokaurane, labdane, phorbol and trachylobane skeletal types. Triterpenoids, either pentacyclic or steroidal, have frequently been reported for *Croton* species. Volatile oils containing mono and sesquiterpenoids, and sometimes also shikimate-derived compounds are not rare in the genus. Several species have been reported as sources of different classes of alkaloids, a fact that enhances considerably the importance of the genus from the medicinal point of view. Phenolic substances have frequently been reported, among which flavonoids, lignoids and proanthocyanidins predominate [18]. Some of the phytochemicals present in different species of *Croton* include 1-5% volatile oil including eugenol, vanillin, crotsparinine, crotoflorine, oblongi-foliol, triterpenic acid, sparsiflorine, dotricontamol, b-amyrin and b-sitosterol [17].

Anticancer activity of different species of *Croton*

Croton tiglium L is a leafy shrub of the Euphorbiaceae familythat is native to Southeastern Asia. The seed oil (croton oil)obtained from this plant or its major active constituent, 12-*O*-tetradecanoylphorbol-13-acetate(TPA), is an irritant and inflammatory agent that has been usedwidely as a tumor promoter (usual dose = 5-16 nmol, twicea week) on the skin of mice previously initiated with 7,12-dimethylbenz(*a*)anthraceneor other polycyclic aromatic hydrocarbons [19-24].TPA at a 10,000-fold lower concentration is an extraordinarilypotent stimulator of differentiation in myeloid leukemia cells*in vitro* [25-28]. In studies with solid tumors, TPA was shown to inhibit the growth,stimulate apoptosis, or enhance differentiation in human tumorcell lines derived from patients with melanoma or prostate,breast, colon, or lung cancer [29-33]. Treatmentof prostate cancer LNCaP cells with clinically achievable concentrationsof TPA (1–1.6 nM) resulted in growth inhibition [29-36], and treatment of these cells with a several foldhigher concentration of TPA caused apoptosis [29,34-36].A synergistic inhibitoryeffect of TPA and ATRA on the growth of cultured prostate cancerLNCaP cells, and an inhibitory effect of TPAor ATRA administration on the growth of well-established LNCaPtumors in immunodeficient mice were observed. Tumor regressions were observedin several of the treated mice, and administration of a combinationof TPA and ATRA to these tumor-bearing mice resulted in sometumor regression in all of the treated animals [37].The molecular mechanisms by which TPA and ATRA synergisticallyinhibit growth and induce apoptosis in LNCaP cells are not known. TPA-dependent increasein TNF-α(tumor necrosis factor- alpha) in LNCaP cells has been observed [38]. Treatmentof

LNCaP cells with a combination of TNF-α and ATRA caused agreater-than-additive inhibitory effect on the growth of thesecells.Recent studies have shown that TNF-α synergized withATRA to induce differentiation in myeloid leukemia cells [39] and apoptosis in glioblastoma cells [40] .The results are consistentwith a mechanistic explanation for the synergistic effect ofTPA+ATRA on LNCaP cell growth via TPA-induced formation of TNF-αthat synergizes with ATRA to inhibit the growth of LNCaP cells [37].

Dehydrocrotonin (DHC) is a diterpene lactone obtained from *Croton cajucara* (Sacaca). Dimethylamide-crotonin (DCR), a DHC derivative, has a similar inhibitory effect on leukemic HL60 cells as its parent compound evaluated by different endpoints of cytotoxicity. DHC and DCR were found to induce apoptosis and terminal differentiation in HL60 cells, thus inhibiting HL60 cell growth [41]. A variety of stimuli can induce cells to undergo apoptosis, with one of the most reproducible inducers being mild oxidative stress following exposure to anticancer agents. Apoptosis involves events mediated by cysteine proteases (caspases) that are classified as initiators (-8, -9 and -12) or executors (-2, -3, -6 and -7). DCR and DHC produced apoptosis partly by oxidative stress-induced lipid peroxidation, which triggered the caspase cascade, that lead to apoptotic cell death in HL60 cells. DCR and DHC triggered apoptosis in HL60 cells probably through cytochrome *c* release and apoptosome formation [42]. The phytochemical investigation proved that only the stem bark of the mature plants is a rich source of trans-dehydrocrotonin (DCTN), the clerodane type diterpene [43]. Phytochemical investigations led to the isolation of the metabolites DCTN (**1**), cajucarinolide (**6**), isocajucarinolide (**7**), *trans*-crotonin (**2**), *trans*-cajucarin B (**3**), *cis*-cajucarin B (**4**), *trans*-cajucarin A (**5**), *N*-methyltyrosine, vanillic acid and 4-hydroxy-benzoic acid. *In vitro* tests using Ehrlich carcinoma cells, natural **6**, **7**, **1** and **2**, showed a significant cytotoxicity with dose dependent responses over a 48 hr culture period. The semi-synthetic cajucarinolide derivatives (**6** and **7**) showed similar antiproliferative activities compared to natural **6** and **7**. The natural clerodanes **3**, **5**, **6** and **7** (natural and semi-synthetic) showed concentration-dependent growth inhibiting activities on cultured K562 leukemia cells [44].

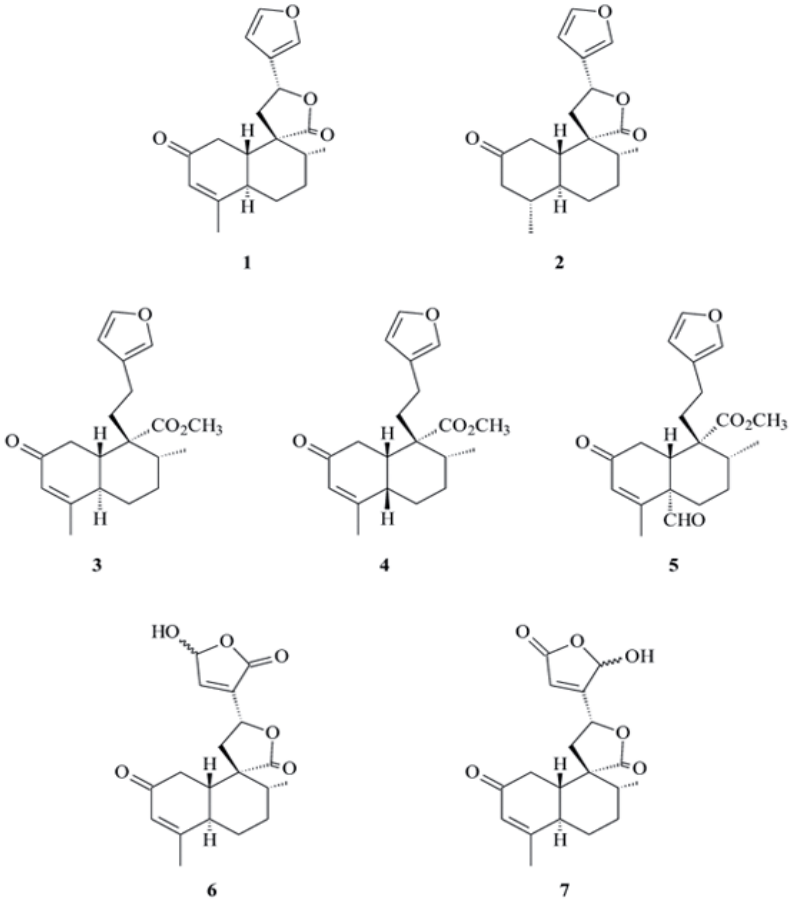


Fig. 2: Metabolites isolated from *Croton cajucara* [44]

Trachylobane diterpenes are secondary metabolites, quite rare in nature, and their bioactivities are poorly understood. ent-trachyloban-3beta-ol isolated from the leaves of *Croton zambesicus*, a plant used in African folk medicine exerts a dose-dependent cytotoxic effect, which varies between cell lines. Induction of apoptosis in HL-60 cells could be detected at a concentration of 50 microM after 24-h treatment. It has been shown that a trachylobane diterpene is able to induce apoptosis in human promyelocytic leukemia cells via caspase-3 activation in a concentration-dependent manner [45].

Four ent-kaurane diterpenoids including two known, ent-7alpha,14beta-dihydroxykaur-16-en-15-one and ent-18-acetoxy-7alpha-hydroxykaur-16-en-5-one, and two new, ent-1beta-acetoxy-7alpha,14beta-dihydroxykaur-16-en-15-one and ent-18-acetoxy-7alpha,14beta-dihydroxykaur-16-en-15-one , isolated from the leaves of *Croton tonkinensis* inhibited LPS(lipopolysaccharide)-induced NF-kappaB(nuclear factor kappa beta) activation in murine macrophage RAW264.7 cells at IC_{50} values between 0.07 and 0.42 microM. Consistently, the ent-kauranoids markedly reduced LPS-induced NO production in a comparable concentration-dependent manner [46].

Three labdane diterpenoids, 2-acetoxy-3-hydroxy-labda-8, 12(*E*)-14-triene, 3-acetoxy-2-hydroxy-labda-8, 12(*E*)-14-triene, and 2,3-dihydroxy-labda-8, 12(*E*),14-triene isolated from stem bark of *Croton oblongifolius*, when tested for cytotoxicity against human tumor cells, the later compound showed non-specific,moderate cytotoxicity whereas the first two compounds were less active [47]. A new furoclerodane, croblongifolin, isolated from the stem bark of *Croton oblongifolius* showed a significant cytotoxicity against various human tumor cell lines including HEP-G2, SW620, CHAGO, KATO3 and BT474 [48].

Two new clerodane diterpenes, crotobrasilin A and crotobrasilin B, have been isolated in addition to four known 3-methoxyflavones: casticin, penduletin, chrysosplenol-D and artemetin from leaves and stems of *Croton brasiliensis* [49]. Two new diterpenes have also been isolated from the aerial parts of *Croton insularis* [50]. As diterpenes from other Croton species have shown anticancer activity, these diterpenes may be investigated to see the anticancer effect if any.

Investigation of the bark of *Croton eluteria* Bennett for biologically active compounds has led to the isolation of the new prenylbisabolane, which proved to be active in selectively inhibiting the induction of NF-κB by tumor necrosis factor-α in T cells [51].

In one of the studies, the methanolic extracts of the roots of *Croton membranaceus* were evaluated for cytoxicity against three human cancer cell lines, DLD-1, MCF-7 and M14 using MTT assay. The root extract exhibited markedly higher cytotoxic activities particularly against the DLD-1 and MCF-7 cells (IC50 = 16.0 and 17.4µg/ml respectively). These results lend some support for the use of this species in traditional medicines for the treatment of cancer [52].

ent-16β-17α-dihydroxykaurane, a compound isolated from barks of *Croton malambo* showed significant cytotoxic and proapoptotic activity on human mammary carcinoma cell line MCF-7 [53].

The anticancer activity of leaf essential oil of *Croton flavens* when tested on lung carcinoma cell line A-549 and human adenocarcinoma cell line DLD-1, was found to be very active against both the tumor cell lines. Three compounds identified in the leaf essential oil ,α-cadinol, β-elemene and α-humulene were cytotoxic against tumor cell lines [54].

Sangre de grado is an ethnomedicinal red tree sap obtained from *Croton palanostigma* ,that is used to treat gastrointestinal ulcers, cancer and to promote wound healing.To evaluate the potential role of sangre de grado (SdG) in cancer ,its effect on human cancer cells, AGS(stomach), HT29 and T84(colon) was cbserved. Cells treated with SdG(100µg/ml) underwent apoptosis as detected by nucleus condensation and DNA fragmentation determined by ELISA, and flow cytometry. A significant alteration of microtubular architecture was equally observed in both stomach and colon cancer cells exposed to SdG(100µg/ml). The induction of apoptosis and microtubule damage in AGS, HT29 and T84 cells suggest that sangre de grado should be evaluated further as a potential source of anti-cancer agent [55].

Dichloromethane and methanol extracts of the roots of *Croton pierrei* Gagnap showed strong cytotoxicity against KB, BC NCI-H187 cell line with ED(effective dose) $_{50}$ of 0.05-4.03µg/ml [56].

In vitro, the essential oil and one of its main constituent, ascaridole from the leaves of *Croton regelianus* displayed cytotoxicity showing IC(50) values in the range of 22.2 to 48.0 microg/ml in HL-60 and SF-295 cell lines for the essential oil, and 6.3 to 18.4 microg/ml in HL-60 and HCT-8 cells lines for ascaridole, respectively. The in vivo study, using sarcoma 180 as a tumor model, demonstrated inhibition rates of 28.1 and 31.8% for essential oil, at 50 and 100 mg/kg, while ascaridole inhibition rates were 33.9% at 10 mg/kg and 33.3% at 20-mg/kg doses. Ascaridole showed an interesting antitumor activity in sarcoma 180 murine model, probably related to cytotoxic activity, and its presence in the essential oil from the leaves of *C. regelianus* could explain, at least in part, the ethnopharmacological use of this plant in the treatment of cancer [57].

The essential oils extracted from the leaves of *Croton matourensis* and flowers and leaves of *Croton micans* were found to have moderate cytotoxicity against LoVo (colon carcinoma), X-17 (colon carcinoma), HeLa (cervical cancer), and control cells [58].

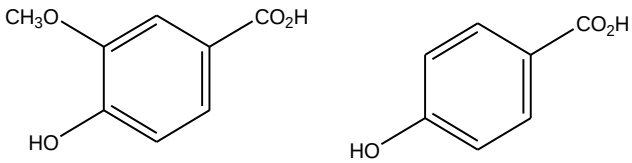
Isoguanosine isolated from *Croton tiglium* showed an antitumor activity against implanted S-180 ascitic tumor mice. It was effective at the dose of 24 mg/kg/day x 5, with T/C value of 168%. Isoguanosine inhibited the growth of S-180 and Ehrlich solid tumor in mice at the optimal doses of 96 mg/kg/day x 12 and 48 mg/kg/day x 12, with 1-T/C values of 65% and 60%, respectively [59].

Methanol extract of the leaves/twigs, roots and stem bark of *Croton argyratus* displayed toxicity to human lung cancer cell lines with an IC50 value of <5.0 µg/ml [60] .

Ethyl acetate extracts of *Croton barorum* and *C. goudotii* showed strong cytotoxic activity, with 100% inhibition at 10 µg/mL in a primary screen using the murine lymphocytic leukemia P388 cell line. Bioassay-guided fractionation led to the isolation of two new 3,4-*seco*-atisane diterpenoids, crotobarin and crotogoudin. Both the compounds produced a net progression in the number of cells arrested at the G2/M growth stage in the cell cycle of the K562 human leukemia cell line at 4 µM.[61]

Antioxidant activity of *Croton*

The sap of *Croton lechleri* , called Dragon's blood, is used in folk medicine as a cicatrizant, anti-inflammatory and to treat cancer. The antioxidant activity of *Croton lechleri* sap when evaluated against the yeast, *Saccharomyces cerevisiae* and against maize plantlets treated with the oxidative agents apomorphine and hydrogen peroxide, it has been found that *Croton lechleri* sap possesses significant antioxidant activity against the oxidative damages induced by apomorphine in *Saccharomyces cerevisiae*. However, in the case of hydrogen peroxide, antioxidant activity of the sap was detected only in cells in the stationary phase of growth. The sap was also able to protect cells of the maize plantlets from the toxic effect of apomorphine[62]. Literature survey revealed that the essential oils from northeastern Brazilian *Croton* species, *Croton zenthmeri*, *Croton nepetaefolius* and *Croton argyrophylloides* exhibited good antioxidant activities [63]. The crude essential oil obtained from the stem bark of *Croton urucurana* exhibited antioxidant properties.The main components of the antioxidant fraction being α-bisabolol, α-eudesmol and guaiol [64].Two of the aromatic acids vanillic and 4-hydroxy-benzoic acid along with N-methyltyrosine have been isolated from *Croton cajucara*. These two aromatic acids have shown remarkable antioxidant activity in other species [65,66]. Based on such results, *C. cajucara* could be expected to possess antioxidant properties. Several kaempferol metabolites have proved to be antioxidant agents [67-69]and *C. cajucara* leaves also contain two of them, e.g. kaempferol 3,4',7-trimethyl ether and 3,7-dimethyl ether.[70]



Vanillic acid 4-Hydroxy-benzoic acid

Fig. 4: Aromatic acids isolated from *Croton cajucara*[44].

The ethanolic extracts obtained from leaf, stem and root of *Croton argyratus* when evaluated for their antioxidant activity by means of 2,2- Diphenyl -1-picrylhydrazyl (DPPH) radical scavenging activity, reducing power and total antioxidant capacity showed that the leaf extract exhibit the highest value of antioxidant activity. The leaf extract also produced the highest total phenolic and total flavonoid content, thus suggesting the potential use of *C. argyratus* plant extracts as a natural source of antioxidant [60].

Croton caudatus has curative medicinal properties for cancer, diabetes, malaria and indigestion. Leaves are claimed to have anticancer property. Phytochemical screening of the crude ethanolic extract of the leaves of *Croton caudatus* revealed the presence of flavonoids, cyanogenetic glycosides, alkaloids and phenolic compounds. Ethanol extract of the leaves of *Croton caudatus* had shown effective antioxidant activity, thus indicating that the leaves of *Croton caudatus* are a potential source of natural antioxidant [71]. Presence of dotriacontamol, bomyrin and b-sitosterol in the roots and barks of the plant have been detected which are used in treatment of ailments related to calcarious (cancer), as per the reports from the Central Drug Research Institute, Lucknow [72].

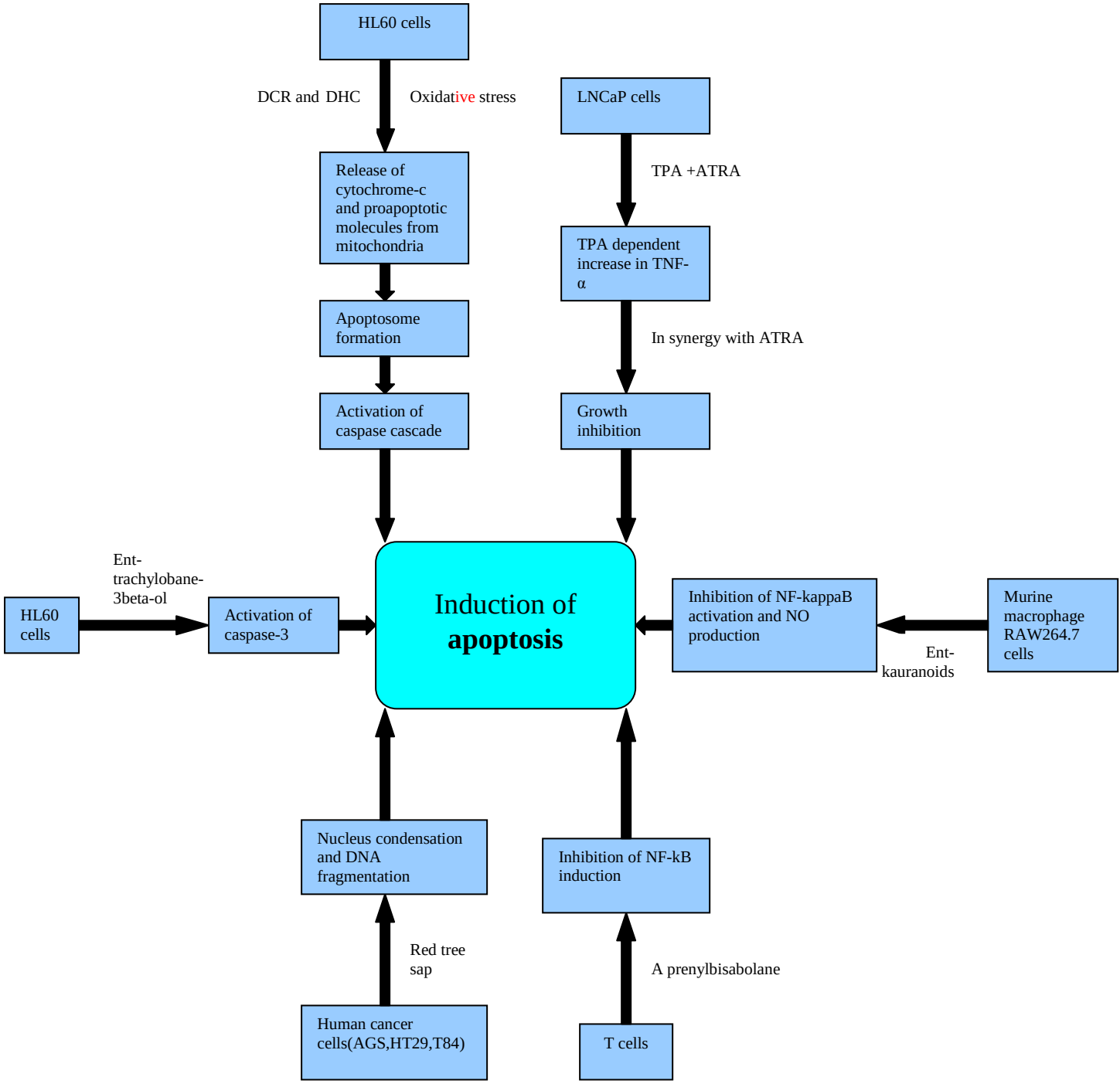


Fig. 3: Integrated scheme of action of anticancer activity shown by natural compounds isolated from some *Croton* species

DISCUSSION

There are considerable scientific evidences to suggest that plant based products can inhibit the process of carcinogenesis effectively. Cancer chemoprevention involves pharmacologic intervention with synthetic or naturally occurring chemical to prevent ,inhibit or reverse carcinogenesis or prevent the development of invasive cancer [73]. Tumor metastasis is the most important cause of death due to cancer, hence various treatment strategies have developed and targeted on preventing the occurrence of metastasis [74]. It is difficult to imagine the possible biochemical mechanism of the anticancer action of diverse groups of natural products. It has been seen that most natural products with anticancer activity act as strong antioxidants and/or modify the activity of one or more protein kinase involved in cell cycle control [8]. Cellular damage caused by reactive oxygen species has been implicated in several diseases and hence antioxidants have significant importance in human health [75].What is needed now is a better understanding of the way in which bioactive substances regulate the activity of enzymes and regulatory molecules such as transcription factors that regulate gene expression, which in turn affects cell proliferation, survival and death. Researches are going on to isolate active components from the crude plant extracts in their pure form and use them at a range of different concentration. This also may improve therapy by removing constituents with opposing activities that may be in the plant extract [8]. A number of important new commercialized anticancer drugs have been obtained from natural sources (herbal sources) by structural modification of natural compounds or by the synthesis of new compounds, designed following a natural compound as model.

Table 1: Different species of *Croton*, their parts used and the extract/compounds isolated with their anticancer/antitumor and antioxidant activity.

Plant	Parts used	Extract/Compound	Bioactivity
C. tiglium	Seed	Seed oil	Induces apoptosis
C. cajucara	Stem bark	(TPA or TPA+ATRA).	in cancer cells. [37]
C. zambesicus	Leaves	Isoguanosine	Antitumor activity. [59]
C. tonkinensis	Leaves	DHC and DCR	Induces apoptosis and cell differentiation.
C.oblongifolius	Stem bark	DCTN , CTN,	[41]
C.eleuteria	Bark	Transcajucarin B,	Cytotoxic activity. [44]
C.membranaceus	Root	Cajucarinolide,	Induces apoptosis in cancer cells. [45]
C.melambo	Bark	Isocajucarinolide,	Reduces LPS induced NO production. [46]
C.flavens	Leaves	Transcajucarin A.	Cytotoxic against tumor cell line. [47,48]
C.pelanostigma	Stem bark	Ent-trachyloban-3beta-ol	Antitumor activity. [51]
C regelianus	leaves	Ent-kuranoids	Cytotoxic against cancer cell line. [52]
***C.pierrei* Gagnep**	Roots	Labdane diterpenoids, Croblongifolin.	Cytotoxic and proapoptotic activity. [53]
C. .matourensis	Leaves	A new prenylbisabolane	Anticancer activity.
C. micans	Leaves, flowers	Crude methanol extract	Cytotoxic against tumor cell line. [54]
C. argyratus	Leaves,roots, stem	Ent-16β-17α-di- hydroxykaurane	Induces apoptosis in cancer cells. [55]
C. lechleri	bark	Essential oil extract (α-cadinol, β-elemene, α-	Cytotoxic activity [57]
C.urucurana	Stem bark	humulene)	Cytotoxic activity. [56]
Baillon	Stem bark	Red tree sap	Antitumor activity [58]
C.caudatus	Leaves	(sangre de grado)	Antitumor activity [58]
		Essential oil (ascaridole)	Cytotoxic [60]
		Dichloromethane and	Antioxidant activity. [62]
		Methanol extract	Antioxidant activity. [64]
		Essential oil	Antioxidant activity. [71]
		Essential oil	
		Ethanol extract	
		Sap	
		Crude essential oil (α-bisabolol,α-eudesmol,guaiol)	
		Ethanol extract	

CONCLUSION

Many medicinal plants have been widely used for the treatment of cancer in traditional way for several generations. *Croton* is one of the largest genera of flowering plants, many species of which are widely used in ethnomedicine for the treatment of several diseases including cancer. As such there has been a growing interest in this genus for phytochemical screening and isolation of anticancer compound/compounds if any. The search for improved cytotoxic agents continues to be an important line in the discovery of modern anticancer drugs. Synergistic interactions of such substances with chemotherapeutic agents may be studied. Also the molecular mechanism of the anticancer activity of the isolated compound/compounds may be a subject of research in near future.

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