

Curcuma Species: A Source of Anticancer Drugs



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Abstract

Cancer is one of the most dreaded diseases which affect people throughout the globe. Treatment of this disease has been a major challenge for the clinicians. With the understanding of the mechanism of cancer development, it was found that lifestyle and food habit is one of the causes of cancer. Herbs and spices are minor constituents of our diet, they have shown to have some medicinal properties with multiple anticancer characteristics. This review focuses on the potential anticancer effects of species of the genus *Curcuma* commonly use as herbs and spices traditionally.

Introduction

Cancer is a complex group of diseases that is characterized by a rapid and uncontrolled formation of abnormal cells, which may mass together to form a growth or tumour, or proliferate throughout the body, initiating abnormal growth at other sites. The development of cancer occurs through a multistage process, which includes initiation, promotion and progression. The transition between the different stages of cancer is driven by endogenous and environmental factors and involves different biochemical mechanism and genetic elements [1]. Cancer is the leading cause of mortality and morbidity worldwide [2]. The main forms of treatment for cancer in humans are surgery, radiation and chemotherapy. Cancer chemo-therapeutic agents can often provide temporary relief of symptoms, prolongation of life, and occasionally cures, but many of them have been shown to cause various side effects [3].

Based on the research findings, phytochemicals and derivatives present in plants are promising options for the improved and less toxic cancer therapy [4]. The National Cancer Institute has identified several commonly used herbs possessing cancer-preventive properties. Those include members of the *Allium* sp. (garlic, onions and chives); members of the Labiatae family (basil, mints, oregano, rosemary, sage, and thyme); members of the Zingiberaceae family (turmeric and ginger); members of the Umbelliferae family (anise, caraway, celery, chervil, cilantro, coriander, cumin, dill, fennel, and parsley) [5]. The focus of this review is on potential anticancer effects of the genus *Curcuma* of the Zingiberaceae family, their anticancer agents and an outline of their possible mechanism of action.

General features of *curcuma*

Curcuma genus is classified under the family Zingiberaceae. The genus contains about 80 species [6]. Their geographical distribution is throughout Southeast Asia, China, India, New Guinea and northern Australia [7]. *Curcuma* is an herbaceous plant with thick, fleshy, rhizomes, pseudo stems and leaf blades. They have flower spikes that arise from the top of the pseudo stem or sometimes on a separate stem directly from the rhizome. Inner part of rhizomes varies in colours, i.e., white, cream, yellow, orange, blue, bluish-green and black [7]. The rhizomes of *curcuma* have been used as a source of food, spice and condiments and as well as medicines [8]. Many of the species of this genus have been used traditionally in the treatment of various diseases and pathological conditions. The following species of *Curcuma* have been studied and reported for their anti-proliferative, apoptotic and anticancer activity.

Curcuma amada

Curcuma amada Roxb is also known as mango ginger since the rhizomes are very similar to ginger but have a raw mango taste. The main use of mango ginger rhizome is in the manufacture of pickles and culinary preparations. The biological activities of mango ginger include antioxidant activity, antibacterial activity, antifungal activity, anti-inflammatory activity, platelet aggregation inhibitory activity, cytotoxicity, an allergic activity, hypotriglyceridemic activity, brine-shrimp lethal activity, enterokinase inhibitory activity, CNS (central nervous system) depressant and analgesic activity [9].

The anticancer property of *Curcuma amada* extracted with different solvent was reported against human large cell lung cancer (NCI-H460) cell [10] and (A-549) human small cell lung carcinoma cells, all the extracts showed comparatively higher toxicity towards cancer cells when compared with normal cells [11]. The anticancer potential and the mechanism of action of a supercritical CO₂ extract of *C amada* in human glioblastoma (U-87MG) cell line demonstrated higher cytotoxicity than temozolomide, etoposide, curcumin and turmeric respectively with specificity towards brain tumour cells.

C amada treatment induced apoptosis in glioblastoma cells in a dose-dependent manner and down regulated genes associated with apoptosis, cell proliferation, telomerase activity, ontogenesis and drug resistance in glioblastoma cells [12]. *C amada* acts through the AKT signalling pathway whereby it inhibits AKT (protein Kinase B) and adenosine monophosphate-activated protein kinase α (AMPK α) phosphorylation, it also down regulates heat shock protein 90 (HSP90) and AMPK α genes. AKT, when deregulated, contribute to the development or promotion of cancer [13]. The anticancer activity exhibited by this herb may be due to the presence of compounds like difurocumenonol and amadaldehyde which have been demonstrated to possess anticancer activity [9,14].

Curcuma aromatica

Curcuma aromatica Salisb is commonly known as wild turmeric. It is a species that stands second among the widely used curcumin species next to common turmeric (*Curcuma longa* Linn.). It has been in traditional use as an aromatic medicinal cosmetic. Some of the pharmacological potentials of wild turmeric and its extracts are anti-inflammatory, wound healing, anti-melanogenic, antioxidant and free radical scavenging activity, anti-repellent, antitussive, anti-platelet activity and antinephrotoxic activity [15].

Aqueous extract of *Curcuma aromatica* was reported to inhibit human colon carcinoma (LS-174-T) cell proliferation. The induction of apoptosis is through both extrinsic and intrinsic pathway by activation of caspases- 8, 9, and 3. The antitumor activity may involve apoptosis and induction of the G₂/M phase arrest via down regulation of cyclin B1 and CDK1 and without the participation of p53 [16]. *Curcuma aromatica* oil showed potential protective mechanism against transformation of esophageal epithelial to esophageal adenocarcinoma (EAC) in rats possibly through its ability to preserve MnSOD (superoxide dismutase) function. Preservation of MnSOD is associated with the potential protective mechanism against transformation of esophageal epithelial to EAC [17].

The main anti-neoplasm ingredient of *C aromatica* is the oils present in the plant with relatively low toxic effects. In vivo studies of the effect of *C aromatica* oil (CAO) in Kunming male mice implanted with hepatoma ascites and C57L/J mice inoculated with mouse liver hepatoma (Hepa1-6) cells an orthotropic HCC mouse model, have reported the significant inhibition of growth of implanted hepatoma in both the model of

study. The inhibition of CAO on the growth of hepatoma might be associated with suppression of PCNA (Proliferating cell nuclear antigen) protein, decreasing DNA-polymerase δ activity and interference with DNA synthesis [18]. Clinically, C aromatic oil was found to be more effective than chemical drugs in treating patients with primary liver cancer through hepatic arterial infusion. Treatment with CAO showed longer survival time and lower toxicity symptoms [19,20].

CAO was found to exhibit an anti-proliferative effect in human hepatocellular carcinoma Hepa1-6 cells by inducing apoptosis. This inhibition of growth by CAO is associated with cell cycle arrest, cytochrome C translocation, caspase-3 activation, poly-ADP-ribose polymerase (PARP) degradation and loss of mitochondrial membrane potential [20]. The anticancer activity of C aromatic is due to the sesquiterpenoids β -elemene, Germacrone and curcumin derivatives which have been reported to have anticancer activity.

Curcuma caesia

Curcuma caesia Roxb is commonly known as black tumeric due to its distinguishable bluish-black rhizome with a bitter and pungent smell. Literature has reported it has anti-inflammatory, hepatoprotective, antioxidant, antiasthmatic, antitumour, stomachic and carminative properties [21]. The anti-proliferative activity of *C caesia* was reported against three human cancer cell lines- (MCF-7) human breast cancer, (HCT-116) human colon cancer and (PA-1) ovarian cancer using the SRB (sulforhodamine B) assay [22].

C caesia showed cytotoxic effect against EAC *in vitro* and antitumour activity in Ehrlich's ascites carcinoma (EAC)-treated mice. *C caesia* methanol extract significantly decreased the tumour volume, tumour weight, viable tumour cell and increased the non-viable tumour cell and lifespan of the EAC bearing control mice. The potential antitumour activity is presumably by its direct cytotoxic effect and antioxidant property. The attenuation of oxidative stress in different tissues of EAC bearing mice decreased the viability of EAC cells [23]. The anticancer property of *C caesia* was reported against diethyl nitrosamine (DEN) induced liver cancer. *C caesia* was able to reduce the number of preneoplastic nodules, attenuated the increased activities of marker enzymes such as AST (aspartate aminotransferase), ALT (alanine aminotransferase), ALP (alkaline phosphatase) and AChE (Acetylcholine esterase) caused by DEN induction, prevent depletion of enzymatic and non enzymatic antioxidant defence system in livers of animals treated with DEN when compared with normal animals.

C caesia may be able to repair hepatic tissue damage caused by tumour induction [24]. *C caesia* also lowered TNF α (tumour necrosis factor- α) level and NF- κ B (nuclear factor- κ B) binding activity in treated mice. It may possess anti-inflammatory, ant proliferative and anti cancer properties and that the active components may exert anticancer effects through the TNF α mediated NF- κ B signalling pathway [25].

Curcuma longa

Curcuma longa is commonly known as turmeric. It is used as a spice, for imparting colour to food and as food preservatives. The herb is used traditionally for a number of different ailments and diseases. It is used against biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis [26]. The therapeutic application of this plant has been thoroughly studied and was shown to have a wide spectrum of biological actions. These include its anti-inflammatory, antioxidant, anticarcinogenic, anticoagulant, antifertility, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, antifibrotic, antivenom, antiulcer, hypertensive and hypocholesterolemic activities [26].

The potential anticancer activity of turmeric was reported by Kuttan et al. [27] in the early 1980; ethanol extract of rhizomes of *Curcuma longa* extract inhibited the cell growth in Chinese Hamster Ovary (CHO) cells and was cytotoxic to lymphocytes and Dalton's lymphoma. Move over, in the same study intraparitoneal injection of liposome encapsulated curcumin inhibited tumour formation and increased survival rate of mice injected with Dalton's lymphoma cells. In a comparative study of 44 plants, *C longa* was found to inhibit the growth of human colon carcinoma cells lines HCT116, SW480, CaCo2, HT29, and SW837, causing a dose-dependent sub-G₁ fraction of cells [28]. *C longa* was also found to inhibit the growth of two leukemic cell lines; myeloid leukemia (U937) and acute lymphoblastic leukemia (Molt4) [29], human lung carcinoma (A549) [30], human cervical cancer cells (HeLa) [31] and murine melanoma cell line (B164A5). Cytotoxic effect of n-hexane extract of *C longa* was reported on (A549) lung cancer cell line and the extract also showed the inhibition of telomerase activity in a dose-dependent manner [32]. A number of compounds have been isolated and characterized from *C longa*.

The main components are curcumin, desmethoxycurcumin, mono demethoxycurcumin, bisdemethoxycurcumin, dihydro curcumin and cyclo curcumin. The anticancer effects of the main component curcumin and its analogs have been thoroughly reviewed by Aggrawal, Pongrakhananon, Perrone et al. [33]. The anticancer activity of other compounds and oils extracted from *C longa* has also been reported. *Curcuma* C20 dialdehyde isolated from *C longa* was reported to suppress the proliferation of HCT116, HT29 and HeLa cells. Exposure to lower concentrations of this compound significantly induced cell cycle arrest at G₁ phase for both HCT116 and HT29 cells, while higher concentrations increased sub-G₁ populations [34-36]. To date, at least 185 compounds of terpenes have been isolated or detected from leaves, flowers, roots and rhizomes of *C longa*, including 68 monoterpenes, 109 sesquiterpenes, five diterpenes, and three triterpenoids. Some of the oils have also been reported for their anticancer activity [37].

Curcuma mangga

Curcuma mangga is used traditionally for stomachic, gastric ulcer, cholic, fever, chest pain. It has antibacterial, analgesic

and hepato protective activity [38]. *C mangga* was reported to inhibit the growth of human breast cancer (MCF-7) and human colorectal adenocarcinoma (HT-29) cell line by MTT proliferation assay. The extract of *C mangga* showed strong cytotoxic effects against EBV-EA induced Raji cells [39]. The cytotoxic activity of *C mangga* hexane and ethyl acetate extract on HT-29 cells was also reported by Hong et al. [40]. The extracts were able to induce early and late apoptosis and arrested the cells at the G₀/G₁ phase. Ethanol extract of *C mangga* also inhibited the growth of human prostate cancer (PC-3) cell lines. It causes down regulation of 5AR1, androgen-receptor and P13K expression along with dihydrotestosterone proteins. *C mangga* inhibited the growth of PC-3 cells partially through down regulation of the 5AR (androgen receptor) pathway [41].

Curcuma purpurascens

C purpurascens is locally known as 'Temu Tis' or 'Solo's in Indonesia. The powdered rhizomes are usually taken together with other herbs to treat ailments, such as cough and skin infections. The herb has been reported to have good antifungal activity [42]. *C purpurascens* was reported to induce apoptosis in (HT-29) human colorectal adenocarcinoma cells by activating the mitochondrial death pathway via the Bcl-2/Bax/Bcl-xl and ROS (reactive oxygen species) production [42]. The rhizome oil was reported to have strong inhibitory effect against HT-29 cells but showed very mild cytotoxicity against HCT-116 cells. Its inhibitory effect against HT-29 cells may be due to the augmentation of COX-2 expression levels by ar-turmerone and synergistic effects of other constituents, such as turmerone, germacrone, germacrene-B, and curlone [43]. In vivo studies of the anticancer effect of *C purpurascens* was reported in azoxymethane (AOM) induced colon cancer of male Sprague-Dawley rats. Dichloromethane extracts of *C purpurascens* decreased the aberrant crypt foci (ACF) formation, and reduced expression of PCNA. The extract upregulated Bax and down regulated Bcl-2 which may induce apoptosis of transformed cells. The extract may have reduced the oxidative stress caused by AOM as shown by the elevated antioxidant enzymatic activity and reduced malondialdehyde level [44].

Curcuma xanthorrhiza

Curcuma xanthorrhiza Roxb is commonly known as 'Temu Lawak' in Malaysia. The rhizome of this herb is similar to ginger with aromatic, pungent odor and bitter taste. *C xanthorrhiza* is reported to be useful for hepatitis, liver complaints, diabetes, rheumatism, hypertension and heart disorders. It has also shown diuretic, anti-inflammatory, anti-oxidant, anti-hypertensive, anti-rheumatic, anti-hepatotoxic, anti-dysmenorrhoeal, antispasmodic, anti-leucorrhoea, anti-bacterial and antifungal effects. It reduces cholesterol, treats constipation, migraines and increases flow of milk during breast feeding [45].

Methanol extract of *C xanthorrhiza* was reported to reduce ornithine decarboxylase expression in mouse skin, reduced the number of tumours and percentage of

occurrences of tumour bearing mice in a multistage skin carcinogenesis induced by 7,12-dimethylbenz[α]anthracene and 12-O-tetradecanoylphorbol-13-acetate [46]. Crude extract of this herb was reported to show antitumour properties against sarcoma180 ascites in mice. The antitumour effect was due to bisabolane sesquiterpenoids; α -curcumene, α -turmerone and xanthorrhizol [47]. The anticancer property of xanthorrhizol had been studied extensively and the compound was reported to have anti-proliferative activities in many types of human breast cancer cells- MDA-MB-231, MDA-MB-453, SK-BR-3, MCF-7, YMB-1 and T47D. Furthermore, the anticancer activities of xanthorrhizol have also been reported in colon cancer, cervical cancer, liver cancer, skin cancer, lung cancer, tongue cancer, oral cancer, esophageal cancer and ovarian cancer. The anticancer mechanisms of xanthorrhizol are comprehensive and diverse by modulating different levels of cellular growth and apoptosis. Its mechanism is closely associated with its antioxidative and anti-inflammatory activities, induction of apoptosis and cell cycle arrest [48].

Curcuma zedoaria

Curcuma zedoaria Rosc is also known as white turmeric. *C. zedoaria* is a well known ethno medicinal plant which is used in the treatment of various forms of diseases such as stomachic, deworming, emmenagogic, vomiting, menstrual haematoma, treatment of leucorrhoea discharge, allergies, dropsy, leprosy, lymphangitis, furunculosis. *C. zedoaria* is reported to have antimicrobial, antifungal, antiamoebic, antinociceptive, antiallergic, antiulcer, antivenom, anti-inflammatory, antimutagenic, antioxidant, analgesic, platelet activating activities, hepatoprotective, hemagglutinating, cytotoxic and larvicidal effect [49]. The cytotoxic activity of *C. zedoaria* was reported against human large cell lung cancer (NCI-H40) [10] *Curcuma zedoaria* exhibited anti-proliferation and invasion activities against (TE-8) human esophageal cancer cells showing specificity towards cancer cells at lower doses.

The induction of apoptosis in TE-8 cells treated with the *C. zedoaria* extract occurred through the caspase cascade-dependent pathways, which involved activation of caspase-9, caspase-3 and PARP along with suppression of Bcl-2 through the Akt/mTOR signalling pathway. *C. zedoaria* upregulated PTEN and down regulated phosphorylated Akt, mTOR (mechanistic target of rapamycin) and STAT3 (Signal transducer and activator of transcription 3) expressions and attenuated the FGFR1 (Fibroblast growth factor receptor 1) and MMP-2 (matrix metalloproteinase-2). Antitumour effect was also examined in xenograft mouse model of human esophageal cancer; it was found that tumour formation in mice was significantly suppressed through the oral administration of the extract [50]. Aqueous extract of *Curcuma zedoaria* was reported to inhibit the metastasis of B16 melanoma cells which leads to a decrease in the number of lung metastatic surface nodules and the extension of life span. The macrophage function-modulating activity by *C. zedoaria* appears to underlie its anti-metastatic activity [51].

Extracts of *C. zedoaria* was also reported to have cytotoxic effect against (SiHa) human cervix squamous cell carcinoma and (HepG2) human liver hepatocellular carcinoma cells [52]. *Curcuma zedoaria* reduce the tumour volume, packed cell volume, viable tumour cell count, normalized haematological parameters and improved the antioxidant defences in Ehrlich's ascites carcinoma (EAC) of mice [53]. A number of compounds isolated from *C. zedoaria* were found to exhibit cytotoxic activity against various cancer cell- α -curcumene isolated from *C. zedoaria* induced apoptosis in SiHa cells [54], sesquiterpenoid compound isocurcumenol showed antitumour effect on A549 (human lung carcinoma), KB (nasopharyngeal carcinoma) and K562 (leukemic cells) as well as the DLA (murine lymphoma) cells [55].

The partially purified polysaccharide showed antitumour effect in mice transplanted with sarcoma 180 cells, whereby it caused a decreased in the tumour size of mouse and prevented the chromosomal mutation [56]. The curcuminoids were reported to inhibit the growth of ovarian carcinoma (OVCAR-3), leukemic (HL-60), S-180 sarcoma, and mouse cervical (U-14) cells [57-59]. Curcumenone and curcumenol displayed strong anti-proliferative activity and were found to induce apoptotic cell death of human breast cancer (MCF-7) cells [60]. Curzerenone and alismol inhibited proliferation of MCF-7, human cervix carcinoma (Ca Ski) and HCT-116 [61].

Conclusion

From the literature survey of different *Curcuma* species, it was found that a number of species have been used traditionally as spices as well as for medical purposes in the treatment of different diseases and ailments. The few species discussed above have been shown to have potential anticancer activity in both *in vitro* and *in vivo* models of cancer. Many active compounds have also been identified from different species of *Curcuma*, the most being from *C. longa*, with some of the active compounds common between various the species. However, the anticancer activity of a number of other species has not been reported as of date. Therefore, based on the current research many of the species of this genus have yet to be explored and screened for their anticancer activity and potential development as anticancer drugs or to be used in combination with other drugs. A detailed study of the mechanism of action is also required to have a better understanding of the therapeutic efficacy and to avoid adverse reaction and side effects when used clinically in humans.

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