Curcuma Species: A Source of Anticancer Drugs

Khetbadei L H Hadem* and Arnab Sen
Division of Animal Health, Indian Council of Agricultural Research, India

Submission: August 11, 2017; Published: August 28, 2017
*Corresponding author: Khetbadei L H Hadem, Division of Animal Health, Indian Council of Agricultural Research, India, Email: khet21@gmail.com

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, hypnotiglyceridemic 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 solvents 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 comparably 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 (AMPKα) phosphorylation, it also down regulates heat shock protein 90 (HSP90) and AMPKα 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 difurocumenol and amadaledehyde 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 orthotopic 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 aromatica* 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 aromatica* is due to the sesquiterpenoids β-elemene, Germacrene and curcumin derivatives which have been reported to have anticancer activity.

**Curcuma caesia**

*Curcuma caesia* Roxb is commonly known as black turmeric 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 antitumor activity 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-κB (nuclear factor-kB) binding activity in treated mice. It may possess anti-inflammatory, antiproliferative and anti cancer properties and that the active components may exert anticancer effects through the TNF α mediated NF-kB 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, anti-fertility, anti-diabetic, antibacterial, antifungal, antiproteasomal, antiviral, anti-fibrotic, antivenom, antilucer, hypertensive and hypcholesterolemic 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 intraparotid 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 colorectal carcinoma cells lines HCT116, SW480, CaCo2, HT29, and SW837, causing a dose-dependent sub-G, 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, Pongrakhaniyanon, 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 HT116, HT29 and HeLa cells. Exposure to lower concentrations of this compound suppressed cell cycle arrest at G₀ phase for both HT116 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, germacrone-B, and culenone [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, hypertensive and heart disorders. It has also shown diuretic, anti-inflammatory, anti-oxidant, anti-hypertensive, anti-rheumatic, anti-hepatotoxic, anti-dysmenorrheal, anti-spasmodic, 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[a]anthracite 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, ar-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 haematomata, treatment of leucorrhoea discharge, allergies, dropsy, leprosy, lymphangitis, furunculosis. C zedoaria is reported to have antimicrobial, antifungal antiamoebic, antinoceptive, antiallergic, antiulcer, antivomem, 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] and C 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 antioxidative 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 decrease in the tumour size of mouse and prevented the chromosomal mutation [56]. The curcuminoids were reported to inhibit the growth of ovarian carcinoma (OVCA-3-3), 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.

References

1. Harris CC (1991) Chemical and physical carcinogenesis: Advances and perspectives for the 1990s. Cancer Res 51(18): 5023s-5044s.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5): E359-E386.
3. Bijauliya RK, Alok S, Singh M, Mishra SB (2017) A comprehensive review on cancer and anticancer herbal drugs. Int J Pharm Sci Res 8(7): 2740-2761.
Curcuma longa

Du

Curcuma aromatica

α

Roxb:

and

ginger

and

effect

tumor

Azadirachta indica

Zingiber officinale

on hepatocellular

Q, et al. (2011) Aqueous extract of

11.

Gastroenterol 6(2): 216-219.

16(2): 515-523.

26(1): 97-104.

109-119.

11: 1-11.

13.

Karmakar L, Dolai N, Suresh KRB, Kar B, Roy SN, et al. (2013) Antitumor activity and antioxidant property of Curcuma caesia against Ehrlich’s ascites carcinoma bearing mice. Pharm Biol 51(6): 753-759.

27.

Koh J, Shin S, Kim Y, Lee HJ, Kim HJ, et al. (2009) Cytotoxicity of methanol extract from Curcuma longa rhizomes on human lung carcinoma cells (A549). Int J Plant Sci Ecol 1(5): 208-212.

25.

Hashim FJ, Shawkat MS, Aljewari H (2013) Anti-cancer effect of Curcuma longa on leukemic cell lines evaluated by apoptosis and comet assay. Int J Pharm Pharm Sci 5(3): 309-315.

23.

Shaikh A M, Shrivastava B, Apte KG, Parab PB, Sharma P, et al. (2016) In-vitro screening of some medicinal plants on breast, ovary and colon cancer cell lines. Int J Pharm Bio Sci 7(2): 11-17.

22.

Sirirugsa P, Larsen K, Maknoi C (2007) The genus Curcuma L. (Zingiberaceae): distribution and classification with reference to species diversity in Thailand. Gardens' Bulletin Singapore 59(2): 203-220.

21.

Chang G, Wu WY (2001) A controlled clinical study between hepatic arterial infusion with embolized curcuma aromatic oil and chemical drugs in treating primary liver cancer. Zhongguo Zhong Xi Yi Jie He Za Zhi 21(3): 165-167.

20.

Li Yan, Shi X, Zhang J, Zhang X, Martin RCG, et al. (2014) Hepatic protection and anticancer activity of curcuma: A potential chemo preventive strategy against hepatocellular carcinoma. Int J Oncol 44(2): 505-513.

19.

Cheng JH, Chang G, Wu WY (2001) A controlled clinical study between hepatic arterial infusion with embolized curcuma aromatic oil and chemical drugs in treating primary liver cancer. Zhongguo Zhong Xi Yi Jie He Za Zhi 21(3): 165-167.

18.

Sahu B, Kenwatt R, Chandrakar S (2016) Medicinal value of Curcuma cassia Roxb: An overview. UK J Pharma Biosci 4(6): 69-74.

17.

Ammon HP, Wahl MA (1991) Pharmacology of Curcuma longa. Planta Med 57(1): 1-7.

16.

Kutan R, Bhanumathy P, Nirmala K, George MC (1985) Potential anticancer activity of turmeric (Curcuma longa). Cancer Lett 29(2): 197-202.

15.

Kaneshiro T, Masumi S, Reika T, Murakami A, Ohigashi H, et al. (2005) Curcumin: Preclinical and clinical studies. Anticancer Res 23(1A): 363-398.

14.

Aggarwal BB, Kumar A, Bharti AC (2003) Anticancer potential of Curcumin: Preclinical and clinical studies. Anticancer Res 23(1A): 363-398.

13.

Kuttan R, Bhanumathy P, Nirmala K, George MC (1985) Potential anticancer activity of turmeric (Curcuma longa). Cancer Lett 29(2): 197-202.

12.

Gonzalez MA, Manebro-Argicil J, Tangarik-Castano V, Liliana Betancur (2010) Synthesis and biological evaluation of [(1)-labdadienedial, derivatives and precursors from Curcuma aromatica (Zingiberaceae)]-sclareolide. Eur J Med Chem 45: 4403-4408.

11.

Curcuma aromatica

Roxb.

exerts anticancer effect by tumor necrosis factor-α-mediated decrease in nuclear factor kappaB binding activity. J Basic Clin Pharm 7(1): 1-11.

10.

Ramachandran C, Lollett, Escalon E, Werner QK, Meldick SJ, et al. (2015) Anticancer potential and mechanism of action of mango ginger (Curcuma amada Roxb.)--a promising spice for phytochemicals and biological activities. J Biosci 36(4): 739-748

9.

Policegoudra RS, Aradhya SM, Singh L (2011) Mango ginger (Curcuma amada Roxb.)--a promising spice for phytochemicals and biological activities. J Biosci 36(4): 739-748.
34. Pongrakhananon V, Rojanasakul Yon (2011) Anticancer Properties of Curcumin, Advances in Cancer Therapy.
35. Perrone D, Ardito F, Giammatempo G, Dioguardi M, Troiano G, et al. (2015) Biological and therapeutic activities, and anticancer properties of curcumin. Exp Ther Med 10(5): 1615-1623.
36. Chaithongyot S, Asgar A, Senawong G, Yowapuy A, Lattmann E, et al. (2015) Anticancer effects of Curcuma C20-Dialdehyde against colon and cervical cancer cell lines. Asian Pac J Cancer Prev 16(15): 6513-6519.
37. Afzal A, Oriqat G, Khan MA, Jose J, Afzal M (2013) Chemistry and biochemistry of terpenoids from Curcuma and related species. JBAPN 3(1): 1-55.
38. Lim TK (2016) In Edible medicinal and non medicinal plant, Modified stems roots and bulbs. 12, Springer International Publication, Switzerland.
39. Kirana C (2003) Potential anticancer activity of rhizomes of ginger species (Zingiberaceae family), University of Adelaide, South Australia.
40. Hong GW, Hong SL, Lee GS, Yacocb H, Malek SN, et al. (2016) Non aqueous extracts of Curcuma mangga rhizomes induced cell death in human colorectal adencarcinoma cell line (HT29) via induction of apoptosis and cell cycle arrest at G1/G0 phase. Asian Pac J Trop Med 9(1): 8-18.
41. Karsono AH, Mayasari O, Tandrasasmita, Tjadrawinata RR (2014) Molecular effects of bioactive fraction of Curcuma mangga (DLBS4847) as a down regulator of 5-e-reductase activity pathways in prostatic epithelial cells. Cancer Manag Res 6: 267-278.
42. Rouhollahi E, Moghadamtousi SZ, Paydar M, Fadaeinasab M, Zahedifard M, et al. (2015) Inhibitory effect of Curcuma purpurascens BI rhizome on HT-29 colon cancer cells through mitochondrial-dependent apoptosis pathway. BMC Complement Altern Med 15: 15.
43. Hong S, Lee G, Rahman SNSA, Hamdi OAA, Awang K, et al. (2014) Essential oil content of the rhizome of Curcuma purpurascens Bl. (Temu Tis) and its anti-proliferative effect on selected human carcinoma cell lines. Sci World J 2014: 7.
44. Rouhollahi E, Moghadamtousi SZ, Al Henhena N, Kunasegaran T, Hasanpourghad M, et al. (2015) The chemopreventive potential of Curcuma purpurascens rhizome in reducing azoxymethane induced aberrant crypt foci in rats. Drug Des Devel Ther 9: 3911-3922.
45. Devaraj S, Imslai I, Ramanathan S, Fei Ym M (2013) In vivo toxicological investigations of standardized ethanolic extract of Curcuma xanthorrhiza Roxb. rhizome. J Nat Prod Plant Resour 3(1): 67-73.
46. Park JH, Park KK, Kim MJ, Hwang JK, Park SK, et al. (2008) Cancer chemo protective effects of Curcuma xanthorrhiza. Phytother Res 22(5): 695-698.
47. Itokawa H, Hirayama F, Funakoshi K, Takeya K (1985) Studies on the antitumor bisabolane sesquiterpenoids isolated from Curcuma xanthorrhiza. Chem Pharm Bull (Tokyo) 33(8): 3488-3492.
48. Oon SF, Nallappan M, Tee TT, Shohaimi S, Kassim NK, et al. (2015) Xanthorrhizol: a review of its pharmacological activities and anticancer properties. Cancer Cell Int 15: 100.
49. Lobo R, Prabhua KS, Shirwaikara A, Shirwaikarb A (2009) Curcuma zedoaria Rosc. (White turmeric): a review of its chemical, pharmacological and ethnomedical properties. J Pharm Pharmacol 61(1): 13-21.
50. Hadisaputri YE, Miyazaki T, Suzuki S, Kubo N, Zuhrotun A, et al. (2015) Molecular characterization of antitumor effects of the rhizome extracts from Curcuma zedoaria on human esophageal carcinoma cells. Int J Oncol 47(6): 2255-2263.
51. Seo W, Hwang J, Kang J, Jin U, Suh S, et al. (2005) Suppressive effect of Zedoaricae rhizoma on pulmonary metastasis of B16 melanoma cells. J Ethnopharmacol 101(3): 249-257.
52. Kim M, Kim J, Hong J, Ji M, Lee Y, et al. (2003) Cytotoxic Activity of the Extracts from Curcuma zedoaria. J Toxicol Pub Health 19(4): 293-296.
53. Pal P, Prasad AK, Chakraborty M, Haldar S, Majumder P, et al. (2015) Evaluation of anti cancer potential of methanol extract of Curcuma zedoaria. Asian J Pharm Clin Res 8(5): 271-275.
54. Shin Y, Lee Y (2013) Cytotoxic Activity from Curcuma zedoaria through mitochondrial activation on ovarian cancer cells. Toxicol Res 29(4): 257-261.
55. Lakshmi S, Padmaja G, Remani P (2011) Antitumour effects of Isocurcumenol isolated from Curcuma zedoaria rhizomes on human and murine cancer cells. Int J Medl Chem, P . 13.
56. Kim KI, Kim JW, Hongetal BS (2000) Antitumor genotoxicity and anticlastogenic activities of polysaccharide from Curcuma zedoaria. Mol Cells 10(4): 392-398.
57. Lien EJ, Li W (1985) In Advances in Chinese Medical Materials Research 5: 433-452.
58. Syu WJ, Shen CC, Don MJ, Ou JC, Lee GH, et al. (1998) Cytotoxicity of curcumins and some novel compounds from Curcuma zedoaria. J Nat Prod 61(12): 1531-1534.
59. Lai EYC, Chyau CC, Mau JL, Chen CC, Lai Y, et al. (2004) Antimicrobial activity and cytotoxicity of the essential oil of Curcuma zedoaria. Am J Chin Med 32(2): 281-290.
60. Hamdi OAA, Rahman SNSA, Awang K, Wahab NA, Looi CY, et al. (2014) Cytotoxic constituents from the rhizomes of Curcuma zedoaria. Scientific World Journal 2014: 321943.
61. Rahman SNSA, Wahab NA, Malek SNA (2013) In Vitro morphological assessment of apoptosis induced by anti-proliferative constituents from the rhizomes of Curcuma zedoaria. Evid Based Complement Alt Med: p. 14.
