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Review Article

A REVIEW OF CINNAMON AS A POTENT ANTICANCER DRUG

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ABSTRACT

Cinnamon is one of the most popular and oldest spices. Several recent studies have found that cinnamon also has anticancer activity. The present work has reported the antineoplastic potential of the spice cinnamon in cancer. Collectively, these data suggest that cinnamon could be proposed as a potent anticancer drug. The bibliographic investigation was carried out during January 2004-December 2014 by analyzing journals and peer-reviewed papers from the last decades. Peer-reviewed articles were indexed by Scopus, PubMed, and Google scholar. Only relevant studies published in English were considered. There were 24 articles that reported the cytotoxic activity of cinnamon on all culture cell lines. About 8 species of *Cinnamomum* have been isolated with their active compounds for cancer cell lines. Based on the reviews of those articles, we conclude that cinnamon has the potential to be further developed as an anticancer agent. In further development, however, not only the research for investigating the anticancer activities, but also research for investigating the safety of cinnamon to the normal cell need to be performed.

Keywords: Review, Cinnamon, Anticancer, *Cinnamomum* species, Cell lines.

INTRODUCTION

Cancer is the second leading cause of death in the United States and The United Kingdom [1]. According to the World Health Organization, more than 1 million cases occur each year and more than half are in developing countries [2]. Cancer (a malignant tumor) occurs when the tumor tissue destructively invades healthy surrounding tissue or when dislodged tumor cells form secondary tumors (metastases) in other organs [3].

Cytotoxic substances that particularly affect proliferating or dividing cells are cytostatics. There are side effects of cytostatic therapy, i.e. loss of hair, gastrointestinal disturbances, nausea-vomiting, lowered resistance to infection, and bone marrow depression. Several modes of action of cytotoxic drugs lead to damage in the mitotic spindle, inhibit deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis, transfer alkyl residues into a covalent bond with DNA alkylating, and interact with topoisomerase enzyme [3].

Attention toward new alternative was invited by the failure of conventional chemotherapy to reduce mortality. Approaches that would reduce morbidity, as well as side effects, were conferred by conventional chemotherapy. As a source of effective anticancer agents, plants play a significant role. About 60% of currently used anti-cancer drugs are derived from natural sources such as plants, marine organisms, and micro-organisms [4-6]. Several studies have been conducted on herbs that possess anticancer properties and have been used as potent anticancer drugs (Table 1).

Cinnamon is one of the most popular and oldest spices. The bark and leaves of cinnamon are often added to food preparations to improve taste and aroma. In addition, this herb has been found to possess potent anti-oxidant, antimicrobial, and antipyretic properties, and has been used in traditional Chinese medicine. Several recent studies have found that cinnamon also contains anticancer activity. However, for the development of cinnamon as the traditional medicine for cancer treatment, further studies are necessary such as elucidation of working mechanisms and characterization of active compounds directly linked with anti-tumor activity.

The present work has addressed the antineoplastic potential of the spice cinnamon in cancer. Collectively, these data suggest that cinnamon could be proposed as a potent anticancer drug [8].

CYTOTOXIC ACTIVITY OF *CINNAMOMUM* SP.

In this review, a bibliographic investigation was carried out during January 2004-December 2014 by analyzing journals and peer-reviewed papers from the last decades. Peer-reviewed articles were indexed by the databases of Scopus, PubMed, and Google Scholar. Only relevant studies published in English were considered. The botanical correct names were mentioned after verification from published literature and Database International Plant Names Index, 2008.

The criteria followed for selection of data in this review consider *in vivo* and *in vitro* cytotoxic activity of all *Cinnamomum* species. Plants, their parts/extracts, and compound isolated from *Cinnamomum* had a cytotoxic effect. Furthermore, detailed information on the research status of 18 *Cinnamomum* species has been discussed. The following keywords were used to search for the literature in the databases: *Cinnamomum* cytotoxic and *Cinnamomum* anticancer. The cytotoxic activity of *Cinnamomum* sp. is shown in Table 2.

THE MECHANISM OF ACTION OF THE ACTIVE COMPOUNDS CINNAMON AS A POTENT ANTICANCER DRUG

Cinnamomum zeylanicum, also known as Ceylon cinnamon (the source of its Latin name, zeylanicum) or "true cinnamon," is a tropical evergreen tree, an indigenous plant in Sri Lanka and grows wildly in Madagascar, India, and Indo-China [33]. The cytotoxic activity of the essential oil from *C. zeylanicum* was evaluated in H-ras active-rat fibroblasts (5RP7) and normal rat fibroblasts (F2408) by 2,5-diphenyltetrazolium bromide assay [25]. Some constituents of the oil that may interfere with ras transformation were indicated by the cytotoxic activity [34]. Isoprenylation of proteins was inhibited by many monoterpenes from essential oils of *Cinnamomum* oil such as limonene and geraniol and 20-benzyloxycinnamaldehyde [35-39].

Cinnamomum burmannii Blume (Lauraceae), a tree-like shrub that is native to Southeast Asia and Indonesia, is used for medicine and making

Table 1: Herbs that have been used as potent anticancer drugs [7]

Herbs	Active compound	Herbs	Active compound
Allamanda cathartica	Allamandin	*Penstemon deutus*	Penstimide
Ipomoea batatas	4-ipomeanol	*Elephantopus elatus*	Elephantopin
Helenium automnale	Helenalin	*Vernonia hymenolepis*	Vernolepin
Acronychia baueri	Acronycine	*Taxus brevifolia*	Taxol
Podophyllum peltatum	α dan β-Peltatin	*Podophyllum peltatum*	Podophyllotoxin
Vinca rosea	Vincristine vinblastine	*Cephalotaxus harringtonia*	Harringtonine, homoharringtonine
Jatropha gossypifolia	Jatrophone	*Daphne mezereum*	Mezerein
Taxodium distichum	Taxodione	*Tripterygium wilfordii*	Tripdiolide, triptolide
Brucea antidysenterica	Bruceantin	*Simarouba glauca*	Glaucarubinone
Holacantha emoryi	Holacanthone	*Marah oreganus*	Cucurbitacin E
Acer negundo	Acer saponin P	*Parquetina nigrescens*	Strophantidin
Acronychia baueri	Acronycine	*Crotalaria spectabilis*	Monocrotaline
Maytenus buchananii	Maytanacine	*Heliotropium indicum*	Indicine-N-oxide
Catharanthus lanceus	Leurosine	*Cyclea peltata*	Tetrandin
Ochrosia elliptica	Ellipticine	*Stereospermum suaveolens*	Lapachol
Ochrosia moculata	9-methoxyellipticin	*Jacaranda caucana*	Jacaranone
Camptotheca acuminata	Camptothecin	*Thalictrum dasycarpum*	Thalicarpin
Colchicum automnale	Colchicine	*Acnistus arborescens*	Withaferin
Steganotaenia araliacea	Steganacin	*Bersama abyssinica*	Hellebrigenin asetat
Bouvardia ternifolia	Bouvardin	*Parquetina nigrescens*	Strophantidin
Combretum caffrum	Combretastatin A-4	*Podophyllum peltatum*	α dan β- Peltatin

Table 2: Cytotoxic activity of *Cinnamomum* sp

Number	*Cinnamomum* Species	Part used	Type of extract	Methods	Result	References
1	*Cinnamomum burmannii* Blume	Stem bark	Methanol extract and main constituent, TCA	Human NPC (NPC/HK1 and C666-1) cell lines	IC_{50} on HK1, extract 108.32±3.43 µg/ml, TCA=2.94±0.17 IC_{50} on C666-1, extract=224.32±3.17 µg/ml TCA=6.30±0.74 µg/ml	[9]
2	*Cinnamomum cassia* Nees Ex Blume	Bark	The aqueous extract	Human cervical carcinoma (SiHa) cell lines	Concentration of 80 µg/ml decreased the kinetics growth of cancer up to 2-fold compared to that observed in the untreated control cells	[10]
3	*Cinnamomum cassia* Nees Ex Blume	Bark	Ethanolic extract and main constituent TCA	Human colorectal carcinoma (HCT 116 and HT 29) cell lines	the cinnamon-derived food factor CA is a potent activator of the Nrf2-orchestrated antioxidant response in cultured human epithelial colon cells	[11]
4	*Cinnamomum cassia* Nees Ex Blume	Bark	Aqueous extract	Tumor cell line lymphoma, melanoma and cervix mouse melanoma model	Cinnamon extract 0.5 mg/ml inhibits tumor cell growth *in vitro* Cinnamon extract 400 µg/g mouse weight has potent anti-tumor activity *in vivo* Anti-tumor effects of cinnamon extracts is mediated by induction of tumor apoptosis through the inhibition of NFκB and the AP1 levels	[12]
5	Cinnamomum cassia, Nees Ex Blume	Bark	Cinnamaldehyde	Hepatoma Hep G2 cells line	IC_{50} cinnamaldehyde=9.76±0.67 µM. Its apoptotic mechanism in Hep G2 cells could be mediated through the tumor protein (p53) induction and CD95, APO-1 signaling pathways	[13]
6	*Cinnamomum cassia*, Nees Ex Blume		Cinnamaldehyde, Cinnamic acid, Cinnamyl alcohol	Human liver cancer (Hep G2) cells line	The best activity is CA with IC_{50}=9.76 µM	[13]
7	*Cinnamomum esmophicum*	Leaves	Essential oil	Human lymphoblast lung (U937), human leukemia (K562), Human liver cancer (Hep-1) cells line	Have cytotoxic effect	[14]
8	*Cinnamomum subavenium* Miq	Leaves	Subamolide D and E, Secusubamolide A.	Human colon adenocarcinoma (SW 480) cell lines	Subamolide D and E caused DNA damage in a dose- and time-dependent manner	[15]
9	*Cinnamomum subavenium* Mig	Stem	Main constituent submolide B	Human SCC12, Epidermoid carcinoma (A431), BCC-1, Human melanoma (A375) cell lines	IC_{50} on A3675=17,59 µg/ml, A431=13,30 µg/ml, BCC-1 ≥20 µg/ml, SCC2=9,12 µg/ml	[16]

(Contd...)

Table 2: ***(Continued)***

Number	*Cinnamomum* Species	Part used	Type of extract	Methods	Result	References
10	*Cinnamomum tenuifolium* Sugim	Stems	Butanolides (tenuifolide A, isotenuifolide A and tenuifolide B), secotenuifolide A tenuifolin	Human prostate cancer cell (DU145) cell lines	Secotenuifolide A induced Noticeable reduction of mitochondrial transmembrane potential; Significant increase in the ratio of cytochrome c concentration (cytosol/mitochondria) and Subsequent activation of caspase-9/ caspase-3	[17]
11	*Cinnamomum zeylanicum* Blume	Leaves	Essential oil	Human cancer cells line	Have cytotoxic effect	[18]
12	*Cinnamomum zeylanicum* Blume	Bark	Essential oil	Human cancer cells line	Have cytotoxic effect	[19] [20] [21]
13	*Cinnamomum zeylanicum* Blume		Aqueous	Promyelocytic leukemia (HL-60) cells line	Have cytotoxic effect	[22]
14	*Cinnamomum zeylanicum* Blume		Ethanolic	Human cancer cells line	Have cytotoxic effect	[23]
15	*Cinnamomum zeylanicum* Blume		Ethanolic	Leukemia cells line	Have cytotoxic effect	[24]
16	*Cinnamomum zeylanicum* Blume	Bark	Essential oil	Rat embryonic fibroblast cells (5RP7) cell lines	IC_{50} 5RP7=15 µg/ml	[25]
17	*Cinnamomum zeylanicum* Blume	Graund	Aqueous extract	VEGFR-2 tyrosine kinase activity	cinnamon extract was a potent inhibitor of VEGFR-2 kinase activity, with an IC_{50} of 30 ng/ml, and showed inhibition of kinase activity with an IC_{50} of 1 lM that could potentially be useful in cancer prevention and/or treatment	[26]
18	*Cinnamomum zeylanicum* Blume	Bark	Petroleum ether and chloroform extract	Human oral cancer (KB) cells line and mouse lymphocytic leukemia (L1210) cells	ED50 PE KB cells=60 L1210 cells 24 pg/ml, KB=58 L1210 cells=20 pg/ml	[27]
19	*Cinnamomum zeylanicum* Blume	Bark	Aqueous	Various cell lines	IC_{50}=0.16 mg/mL	[8]
20	*Cinnamomum kotoense* Kaneh and Sasaki	Leaves	Kotomolide A (1), isokotomolide A (2), and kotomolide B (3), and a new secobutanolide, secokotomolide A (4)	Human epithelioid cervix carcinoma (HeLa) cell lines	secokotomolide A induced (a) noticeable reduction of mitochondrial transmembrane potential (DeltaPsi (m)), (b) activation of caspase 3/7, and (c) up-regulation of the p53 expression. These results suggest that an increase of Hydrogen peroxidase (H_2O_2) and/or peroxide by compound 4 is the initial apoptotic event	[28]
21	*Cinnamomum tamala* T.Nees and Ebrem	Leaves	Ethanol extract	Artemia salina (Brine shrimp)	LC_{50}=40 µg/ml	[29]
22	*Cinnamomum verum* J.Presl	fresh and dry barks	Acetone and methanolic extracts	Breast cancer cell line (MCF7) cell lines	Acetone extract show LD_{50}=19,74 µg/ml methanolic extract=14,98 µg/ml	[30]
23	*Cinnamomum verum* J.Presl and *Cinnamomum tamala* T.Nees and Ebrem	*Cinnamomum verum* (bark) and *Cinnamomum tamala* (Indian bay leaf)	Methanol extract	Prostatic SCC (PC-3) cell line, Human glioblastoma multiforme tumor (T98G) cell lines	The bark methanol extract *Cinnamomum verum* showed potential activity greater than *Cinnamomum tamala*. *Cinnamomum verum* against prostrate (PC-3) and glioblastoma (T98G) cancer cell lines with 90% and 78% growth inhibition at 100 µg/ml concentration respectively	[31]
24	*Cinnamomum osmophloeum* Kaneh	bark and roots	(E) feruloyl ester	Human liver cancer (Hep G2 and Hep3B): human oral squamous cell carcinoma (Ca9-22) cells	IC_{50} values=7.87 µg/mL (Hep G2), 4.31 µg/mL (Hep3B), and 2.51 µg/mL (Ca9-22)	[32]

TCA: Trans-cinnamaldehyde, CA: Cinnamic aldehyde, Nrf: Nuclear-related factor, NFκB: Nuclear factor kappa B, AP1: Activator protein 1, APO-1: Apoptosis antigen-1, CD: Cluster of differentiation, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, VEGFR-2: Vascular endothelial growth factor receptor-2, ED50: Effective dose 50, NPC: Nasopharyngeal carcinoma

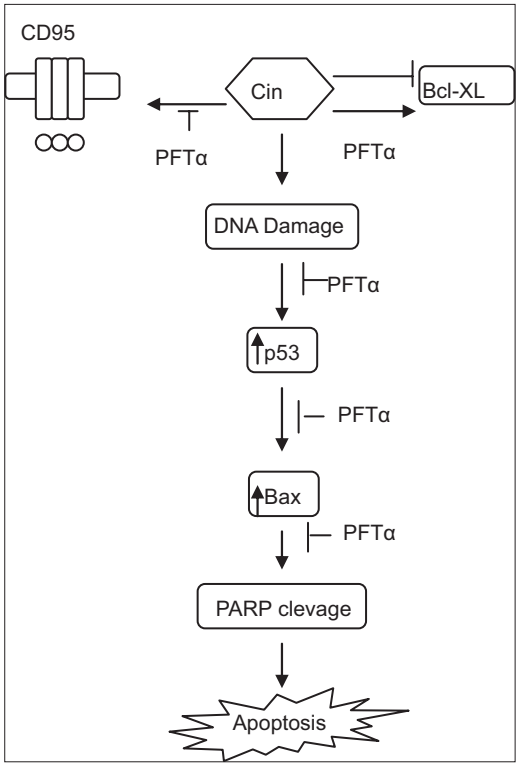

Figure 1 : A proposed model for the cytotoxic mechanisms of action of Cinnamaldehyde [13]

spices for the flavor industry [40,41]. Trans-cinnamaldehyde (TCA) has been identified as one of the bioactive compounds in *C. burmannii* [42]. In addition, studies have demonstrated that TCA inhibits cell proliferation and induces cell apoptosis (Fig. 1) [13,43-45]. The anti-neoplastic potential of the methanol extract of the *C. burmannii* stem and its constituent, TCA, showed the cytotoxicity on HK1 and C666-1 nasopharyngeal carcinoma (NPC) cell lines [46].

Cinnamomum cassia Presl is widely cultivated in China. The dried stem bark of *C. cassia*, i.e., cassia bark, is not only important as a food spice, but is also considered to have medicinal properties and contains large amounts of bioactive compounds including essential oils (cinnamic aldehyde and cinnamyl aldehyde), tannin, mucus, and carbohydrates [47].

An antitumor effect of cinnamon was previously suggested *in vitro* [47,48] without *in vivo* evidence or a working mechanism. Elucidation of its mechanism of action will be important for its use as a traditional medicine [49]. In anticancer study, CA was active against human liver, lung, and leukemia cancer cells [19-21]. CA has been shown to possess antitumor activity through inhibiting cell proliferation and inducing cell apoptosis [43,50,51]. Its inhibitory effect on cell cycle progression was demonstrated through its ability to induce S-phase arrest in human PLC/PRF/5 cells [43]. The effect of CA on Hep G2 cell apoptosis was concluded on the CD95 (APO-1/CD95) signal transduction and p53 pathways. Several studies have shown that the B-cell lymphoma 2 (Bcl-2) family of proteins is the central of apoptotic regulation [52,53].

Cinnamomum subavenium Miq. (Lauraceae) is a medium-sized evergreen tree distributed in Burma, Cambodia, Central and Southern parts of China, Indonesia, Malaysia, and Taiwan [54]. Subamolide B is a butanolide isolated from *C. subavenium* Miq. Subamolide A, an isomer of subamolide B, has been reported to induce apoptosis in human colon adenocarcinoma cell line SW480 and human urothelial carcinoma cell line NTUB1 in addition to acting as an inhibitor of human tyrosinase [54-58]. Furthermore, an *in vitro* antimelanoma activity has been assigned to subamolide E, another butanolide isolated from *C. subavenium* [58,59].

Subamolide B activates the cell death pathways which were mediated by type II transmembrane protein (FasL/Fas), mitochondria, and endoplasmic reticulum stress. These cell death pathways lead to the activation of caspase-8, caspase-9, caspase-4, and caspase-3 (Fig. 2) [58].

Cinnamomum kotoense is a small evergreen tree, endemic to Lanyu Island of Taiwan and recently has been cultivated as an ornamental plant. The extracts of *C. kotoense* effects on anti-proliferation activity on human peripheral blood mononuclear cells [59] and antitumor activity against HeLa cell [28]. Isoobtusilactone A was isolated from the *C. kotoense* leaves that was able to exhibit cytotoxic and genotoxic effects on a variety of cell types, including human laryngeal carcinoma Hep-2, Chinese hamster ovarian cell CHO-K1, rat hepatoma tissue culture [60], and mouse lymphoid leukemia P-388 [61].

Cinnamomum tenuifolium Sugimoto form. nervosum (Meissn.) Hara. (Lauraceae) is a medium-sized evergreen tree endemic to the Lanyu Island of Taiwan, all plant parts being conspicuously free of cinnamon odor. A methanol extraction of the stems of *C. tenuifolium* afforded tenuifolide A, isotenuifolide A [17], tenuifolide B [62], and secotenuifolide A [57].

Cinnamomum tamala is a moderate-sized evergreen tree attaining a height of 8 m, and a girth of 150 cm. *C. tamala* is found in tropical and sub-tropical Himalayas, Khasi and Jaintia hills, and in Eastern Bengal, India.

Cinnamomum verum J. Presl is an evergreen tree, 10-15 m tall, belonging to the family Lauraceae and is native to Sri Lanka and South India. CA, one of the components in the bark has been found to possess significant antitumor, cytotoxic effect [12].

Cinnamomum osmophloeum Kaneh is an endemic tree of Taiwan. It grows in the natural hardwood forest elevations between 400 and 1500 dpi. CA, a major bioactive compound isolated from the leaves of *C. osmophloeum* Kaneh [63,64], has been known to trigger apoptosis through mitochondrial permeability transition in human promyelocytic leukemia HL-60 cells [65] by activating the proapoptotic Bcl-2 family proteins [43].

CONCLUSION

Review of literatures indicates that *Cinnamomum* showed various cytotoxic activities in cancer cell line, namely basal cell carcinoma, breast cancer (MCF7) cell lines, epidermoid carcinoma (A431), human cancer promyelocytic leukemia (HL-60), human cervical carcinoma (SiHa), human colorectal carcinoma (HCT 116, HT 29, and SW 480), human epithelioid cervix carcinoma (HeLa), human glioblastoma multiform tumor (T98G), human leukemia (K562) and leukemia rat embryonic fibroblast (5RP7), human liver cancer (Hep-1), human lymphoblast lung (U937), human melanoma (A375) cell lines, human NPC (NPC/HK1 and C666-1), human oral cancer (KB) lymphocytic leukemia (L1210) cells, human oral squamous cell carcinoma (SCC) (Ca9-22 and SCC12), human prostate cancer cell (DU145 and PC-3), tumor cell line lymphoma melanoma, and cervix hepatoma Hep G2 cells line (Hep G2 and Hep3B) cell lines.

Literature indicates that when screening various plant extracts, herbs, and other compounds as cytotoxic activity, there were kotomolide A (1), isokotomolide A (2), and kotomolide B (3), and a new secobutanolide, secokotomolide A from *C. subavenium*. Tenuifolide A, isotenuifolide A [17], tenuifolide B [63], and secotenuifolide A from *C. tenuifolium*. Isoobtusilactone A was isolated from the *C. kotoense*. TCA has been identified as one of the bioactive compounds in *C. burmannii*.

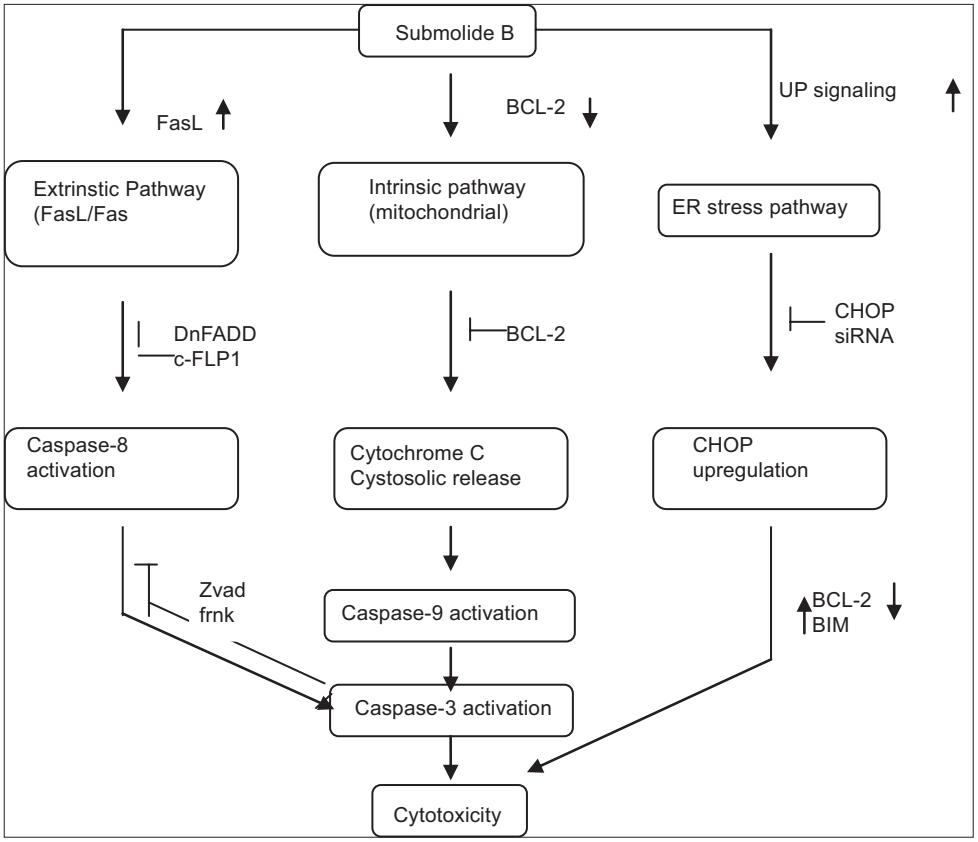

Fig. 2: A proposed model for the cytotoxic mechanisms of action of subamolide B [58]

Based on the review of researches which have been reported by distinguish researchers before, we concluded that cinnamon has the potential to be developed as anticancer, however further researches are needed to confirm the activity as well as the safety of this plants. Some investigations on the anticancer effect of this plant are in progress in our labs.

REFERENCES

1. Dipiro JT. Pharmacotheraphy: Pathophysiology Approach. 7th ed. New York: Mc-Graw Hill Medical Publishing Division; 2008.
2. Aapro M, Abraham I, MacDonald K, Soubeyran P, Foubert J, Bokemeyer C, *et al.* Intraclass correlation metrics for the accuracy of algorithmic definitions in a computerized decision support system for supportive cancer care. Support Care Cancer 2007;15(11):1325-9.
3. Heinz L, Klaus M, Albrecht Z, Detlef B. Color Atlas of Pharmacology. 2nd ed. New York: Thieme Stuttgart; 2000.
4. Rocha AB, Lopes RM, Schwartsmann G. Natural products in anticancer therapy**.** Curr Opin Pharmacol 2001;1:364-9.
5. Mann J. Natural products in cancer chemotherapy: Past, present and future**.** Nat Rev Cancer 2002;2:143-8.
6. Deorukhkar A, Krishnan S, Sethi G, Aggarwal BB. Back to basics: how natural products can provide the basis for new therapeutics. Expert Opin Investig Drugs 2007;16(11):1753-73.
7. Wiart C. Ethnopharmacology of Medicinal Plant Asia and The Pacific. New York: Humana Press; 2006. p. 155-205.
8. Singh R, Koppikar SJ, Paul P, Gilda S, Paradkar AR, Kaul GR. Comparative analysis of cytotoxic effect of aqueous cinnamon extract from *Cinnamomum zeylanicum* bark with commercial cinnamaldehyde on various cell lines. Pharm Biol 2009;47:1174-9.
9. Daker M, Lin VY, Akowuah GA, Yam MF, Ahmad M. Inhibitory effects of *Cinnamomum burmannii* Blume stem bark extract and trans-cinnamaldehyde on nasopharyngeal carcinoma cells; synergism with cisplatin. Exp Ther Med 2013;5(6):1701-9.
10. Koppikar SJ, Choudhari AS, Suryavanshi SA, Kumari S, Chattopadhyay S, Kaul-Ghanekar R. Aqueous cinnamon extract (ACE-c) from the bark of *Cinnamomum cassia* causes apoptosis in human cervical cancer cell line (SiHa) through loss of mitochondrial membrane potential. BMC Cancer 2010;10:210.
11. Georg TW, Nicole FV, Sarah DL, Alexandra SB, Tao J, Donna DZ. The cinnamon-derived dietary factor cinnamic aldehyde activates the Nrf2-Dependent antioxidant response in human epithelial colon cells. Molecules 2011;15(5):3338-55.
12. Kwon HK, Hwang JS, So JS, Lee CG, Sahoo A, Ryu JH, *et al.* Cinnamon extract induces tumor cell death through inhibition of NFkappaB and AP1. BMC Cancer 2010;10:392.
13. Ng LT, Wu SJ. Antiproliferative activity of *Cinnamomum cassia* constituents and effects of pifithrin-alpha on their apoptotic signaling pathways in hep G2 cells. Evid Based Complement Alternat Med 2011;2011:492148.
14. Wang M, Shengmin S, Hwang LS, Ho CT. Herbs: Challenges in Chemistry and Biology. ACS Symposium Series; 2006. p. 299-313.
15. Kuo SY, Hsieh TJ, Wang YD, Lo WL, Hsui YR, Chen CY. Cytotoxic constituents from the leaves of *Cinnamomum subavenium.* Chem Pharm Bull (Tokyo) 2008;56:97-101.
16. Yang SY, Wang HM, Wu TW, Chen YJ, Shieh JJ, Lin JH, *et al.* Subamolide B isolated from medicinal plant *Cinnamomum subavenium* induces cytotoxicity in human Cutaneous squamous cell carcinoma cells through mitochondrial and CHOP-dependent cell death pathways. Evid Based Complement Alternat Med 2013;2013:630415.
17. Lin RJ, Cheng MJ, Huang JC, Lo WL, Yeh YT, Yen CM, *et al.* Cytotoxic compounds from the stems of *Cinnamomum tenuifolium*. J Nat Prod 2009;72(10):1816-24.
18. Zu Y, Yu H, Liang L, Fu Y, Efferth T, Liu X, *et al.* Activities of ten essential oils towards *Propionibacterium acnes* and PC-3, A-549 and MCF-7 cancer cells. Molecules 2010;15(5):3200-10.
19. Moon KH, Pack MY. Cytotoxicity of cinnamic aldehyde on leukemia L1210 cells. Drug Chem Toxicol 1983;6(6):521-35.
20. Imai T, Yasuhara K, Tamura T, Takizawa T, Ueda M, Hirose M, *et al.* Inhibitory effects of cinnamaldehyde on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung carcinogenesis in rasH2 mice. Cancer Lett 2002;175(1):9-16.
21. Wu SJ, Ng LT. MAPK inhibitors and pifithrin-alpha block cinnamaldehyde-induced apoptosis in human PLC/PRF/5 cells. Food Chem Toxicol 2007;45(1):2446-53.
22. Assadollahi V, Parivar K, Roudbari NH, Khalatbary AR, Motamedi M, Ezatpour B, *et al.* The effect of aqueous cinnamon extract on the

apoptotic process in acute myeloid leukemia HL-60 cells. Adv Biomed Res 2013;2(12):25.
23. Rao YK, Fang SH, Tzeng YM. Differential effects of synthesized 2'-oxygenated chalcone derivatives: Modulation of human cell cycle phase distribution. Bioorg Med Chem 2004;12(10):2679-86.
24. South J. The body and mind energizer. Vitam Res News 2004;12:800-77.
25. Unlu M, Ergene E, Unlu GV, Zeytinoglu HS, Vural N. Composition antimicrobial activity and *in vitro* cytotoxicity of essential oil from *Cinnamomum zeylanicum* Blume (Lauraceae). Food Chem Toxicol 2010;48:3274-80.
26. Lu J, Zhang K, Nam S, Anderson RA, Jove R, Wen W. Novel angiogenesis inhibitory activity in cinnamon extract blocks VEGFR2 kinase and downstream signaling. J Carcinog 2010;31:481-8.
27. Mu C, Picha P, Rienkijkan M, Preechanukool K. The cytotoxic effect of petroleum ether and chloroform extracts from ceylon cinnamon (*Cinnamomum zeylanicum* Nees) barks on tumor cells *in vitro*. Int J Crude Drug Res 2004;22:177-80.
28. Chen CH, Lo WL, Liu YC, Chen CY. Chemical and cytotoxic constituents from the leaves of *Cinnamomum kotoense*. J Nat Prod 2006;69(6):927-33.
29. Rahman M, Khatun A, Monirul MI, Akter MN, Chowdhury SA, Ahad AK, *et al*. Evaluation of antimicrobial, cytotoxic, thrombolytic, diuretic properties and total phenolic content of *Cinnamomum tamala*. Int J Green Pharm 2013;7:236-43.
30. Rani NP, Venkatesan J, Binilraj SS, Sashidaran I, Amma PK. Antioxidant and cytotoxic potential of acetone and methanolic extracts of fresh and dry barks of *Cinnamomum verum in vitro* study. Cell Tissue Res 2010;20:2131-8.
31. Sudan R, Baghat M, Gupta S, Citrarakha, Devi T. Comparative analysis of cytotoxic and antioxidant potential of edible *Cinnamomum verum* (bark) and *Cinnamomum tamala* (Indian bay leaf). Reed Elsevier India 2013;6:24-32.
32. Chen TH, Huang YH, Lin JJ, Liau BC, Wang SY, Wu YC, *et al.* Cytotoxic lignan esters from *Cinnamomum osmophloeum*. Planta Med 2010;76(6):613-9.
33. Panarama PA, Wimalasena S, Jayatilake GS, Jayawardena AL, Senanayake UM, Mubarak A. A comparison of essential oil constituents of bark, leaf root and fruit of cinnamon (*Cinnamomum zeylanicum*) grown in Sri Lanka. J Natl Sci 2010;29:147-53.
34. Zeytinoglu H, Incesu Z, Baser KH. Inhibition of DNA synthesis by carvacrol in mouse myoblast cells bearing a human N-Ras oncogene. Phytomedicine 2003;10:292-9.
35. Crowell PL. Prevention and therapy of cancer by dietary monoterpenes. J Nutr 1999;129(3):775S-8.
36. Gelb MH, Tamanoi F, Yokoyama K, Ghomashchi F, Esson K, Gould MN. The inhibition of protein prenyltransferases by oxygenated metabolites of limonene and perillyl alcohol. Cancer Lett 1995;91(2):169-75.
37. Moon EY, Lee MR, Wang AG, Lee JH, Kim HC, Kim HM, *et al.* Delayed occurrence of H-Ras12V-induced hepatocellular carcinoma with long-term treatment with cinnamaldehydes. Eur J Pharmacol 2006;530(3):270-5.
38. Gould MN, Moore CJ, Zhang R, Wang B, Kennan WS, Haag JD. Limonene chemoprevention of mammary carcinoma induction following direct *in situ* transfer of v-Ha-Ras. Cancer Res 1994;54(13):3540-3.
39. Carnesecchi S, Bras-Gonçalves R, Bradaia A, Zeisel M, Gossé F, Poupon MF, *et al.* Geraniol, a component of plant essential oils, modulates DNA synthesis and potentiates 5-fluorouracil efficacy on human colon tumor xenografts. Cancer Lett 2004;215(1):53-9.
40. Cao H, Graves DJ, Anderson RA. Cinnamon extract regulates glucose transporter and insulin-signaling gene expression in mouse adipocytes. Phytomedicine 2010;17(13):1027-32.
41. Bandar E. Pharmaceutical applications and phytochemical profile of *Cinnamomum burmannii*. Pharmacogn Rev 2012;6:125-31.
42. Lv GP, Huang WH, Yang FQ, Li J, Li SP. Pressurized liquid extraction and GC-MS analysis for simultaneous determination of seven components in *Cinnamomum cassia* and the effect of sample preparation. J Sep Sci 2010;33(15):2341-8.
43. Wu SJ, Ng LT, Lin CC. Cinnamaldehyde-induced apoptosis in human PLC/PRF/5 cells through activation of the proapoptotic Bcl-2 family proteins and MAPK pathway. Life Sci 2005;77(8):938-51.
44. Zhang JH, Liu LQ, He YL, Kong WJ, Huang SA. Cytotoxic effect of trans-cinnamaldehyde on human leukemia K562 cells. Acta Pharmacol Sin 2010;31(7):861-6.
45. Cabello CM, Bair WB 3rd, Lamore SD, Ley S, Bause AS, Azimian S, *et al.* The cinnamon-derived Michael acceptor cinnamic aldehyde impairs melanoma cell proliferation, invasiveness, and tumor growth. Free Radic Biol Med 2009;46(2):220-31.
46. Dickey JS, Redon CE, Nakamura AJ, Baird BJ, Sedelnikova OA, Bonner WM. H2AX: Functional roles and potential applications. Chromosoma 2009;118(6):683-92.
47. Schoene NW, Kelly MA, Polansky MM, Anderson RA. Water-soluble polymeric polyphenols from cinnamon inhibit proliferation and alter cell cycle distribution patterns of hematologic tumor cell lines. Cancer Lett 2005;230(1):134-40.
48. Kamel CA. Novel look at a classic approach of plant extracts. Feed Mix Spec 2000;249:19-25.
49. Kwon HK, Jeon WK, Hwang JS, Lee CG, So JS, Park JA, *et al.* Cinnamon extract suppresses tumor progression by modulating angiogenesis and the effector function of $CD8^+$ T cells. Cancer Lett 2009;278(2):174-82.
50. Wu SJ, Ng LT, Lin CC. Effects of vitamin E on the cinnamaldehyde-induced apoptotic mechanism in human PLC/PRF/5 cells. Clin Exp Pharmacol Physiol 2004;31(11):770-6.
51. Kwon BM, Lee SH, Choi SU, Park SH, Lee CO, Cho YK, *et al.* Synthesis and *in vitro* cytotoxicity of cinnamaldehydes to human solid tumor cells. Arch Pharm Res 1998;21(2):147-52.
52. Cory S, Adams JM. The Bcl2 family: Regulators of the cellular life-or-death switch. Nat Rev Cancer 2002;2(9):647-56.
53. Yu W, Sanders BG, Kline K. RRR-alpha-tocopheryl succinate-induced apoptosis of human breast cancer cells involves Bax translocation to mitochondria. Cancer Res 2003;63(10):2483-91.
54. Chen CY, Chen CH, Wong CH. Cytotoxic constituents of the stems of *Cinnamomum subavenium*. J Nat Prod 2007;70:103-6.
55. Liu CH, Chen CY, Huang AM, Li JH. Subamolide A, a component isolated from *Cinnamomum subavenium*, induces apoptosis mediated by mitochondria-dependent, p53 and ERK1/2 pathways in human urothelial carcinoma cell line NTUB1. J Ethnopharmacol 2011;137(1):503-11.
56. Wang HM, Chiu CC, Wu PF, Chen CY. Subamolide E from *Cinnamomum subavenium* induces sub-G1 cell-cycle arrest and caspase-dependent apoptosis and reduces the migration ability of human melanoma cells. J Agric Food Chem 2011;59(15):8187-92.
57. Kuo PL, Chen CY, Tzeng TF, Lin CC, Hsu YL. Involvement of reactive oxygen species/c-Jun NH(2)-terminal kinase pathway in kotomolide A induces apoptosis in human breast cancer cells. Toxicol Appl Pharmacol 2008;229(2):215-26.
58. Wang HM, Chen CY, Wen ZH. Identifying melanogenesis inhibitors from *Cinnamomum subavenium* with *in vitro* and *in vivo* screening systems by targeting the human tyrosinase. Exp Dermatol 2011;20(3):242-8.
59. Kuo SY, Hsieh TJ, Wang YD, Lo WL, Hsui YR, Chen CY. Cytotoxic constituents from the leaves of *Cinnamomum subavenium*. Chem Pharm Bull 2005;56:97-101.
60. Garcez FR, Garcez WS, Martins M, Matos MF, Guterres ZR, Mantovani MS, *et al.* Cytotoxic and genotoxic butanolides and lignans from *Aiouea trinervis*. Planta Med 2005;71(10):923-7.
61. Tsai IL, Hung CH, Duh CY, Chen IS. Cytotoxic butanolides and secobutanolides from the stem wood of Formosan *Lindera communis*. Planta Med 2002;68(2):142-5.
62. Chen CY, Chen CH, Lo YC, Wu BN, Wang HM, Lo WL, *et al.* Anticancer activity of isoobtusilactone A from *Cinnamomum kotoense*: Involvement of apoptosis, cell-cycle dysregulation, mitochondria regulation, and reactive oxygen species. J Nat Prod 2008;71(6):933-40.
63. Cheng SS, Liu JY, Tsai KH, Chen WJ, Chang ST. Chemical composition and mosquito larvicidal activity of essential oils from leaves of different *Cinnamomum osmophloeum* provenances. J Agric Food Chem 2004;52(14):4395-400.
64. Cheng SS, Liu JY, Hsui YR, Chang ST. Chemical polymorphism and antifungal activity of essential oils from leaves of different provenances of indigenous cinnamon (*Cinnamomum osmophloeum*). Bioresour Technol 2006;97(2):306-12.
65. Ka H, Park HJ, Jung HJ, Choi JW, Cho KS, Ha J, *et al.* Cinnamaldehyde induces apoptosis by ROS-mediated mitochondrial permeability transition in human promyelocytic leukemia HL-60 cells. Cancer Lett 2003;196(2):143-52.