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An Abrust- for Anticancer Plants Inducing Apoptosis.

Biba Veerabhadran Sobhana

1.Sangeetha Sugathan, Jestin Kunjumol George. and Remani Prathapan. Division of Cancer Research, Regional Cancer Centre, Thiruvananthapuram, Kerala, India. 695011.

ABSTRACT

Traditional medicines have been recently recognized as a precise and knowledge for new source of anticancer drugs and new chemotherapy adjuvant to enhance the efficacy of chemotherapy and to ameliorate the side effects of cancer chemotherapies however their healing mechanisms are still largely unknown. The current available methods of treatment like chemotherapy, radiation, and surgery can induce certain side effects, so there is urge for alternate or adjuvant therapies has arisen. The natural compounds present in plants were known to inhibit or kills carcinogenic cells. In the race for the designing of new anti-cancer drugs development the phytochemical investigation of herbs has contribute new ideas in some extent. Apoptosis is the programmed cell death in which the cells activate an intracellular death program and kill themselves in a controlled way. The phytochemicals that have the anticancer property by inducing apoptosis are safe, abundantly available from dietary sources and the drugs have good immunomodulatory properties. This attempt has been made to review plant and plant products used in the prevention and treatment of cancer by inducing apoptosis.

Keywords: Traditional medicine, Medicinal plants, Phytochemicals, Apoptosis.

*Corresponding Author Email: vsbiba@gmail.com

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INTRODUCTION

Cancer

Nowadays cancer is used as a generic term describing a group of almost 120 different diseases, which can affect any part of the body and defined as uncontrolled growth and invasion of normal tissues and spread of cells[1]. Cancer statistics indicate that most common new cancer cases (excluding common non-melanoma skin cancer) include lung, breast, colorectum, stomach, prostate and liver. These statistics are affected by a few factors including the increase in the number of carcinogens in daily life conditions (food, alcohol, tobacco etc.; high levels of chemicals and pollutants in environment, exposure to UV and ionizing radiation and viruses), genetic disposition[1] but also higher effectiveness of the treatment regimes. The number of recognized carcinogens (agents, mixtures, oncoviruses, environmental factors) increased day by day [1].

Cancer (proper medical name - malignant neoplasm) commonly considered to be a civilization disease, has in fact been traced to occur even before the ancestral species of man [2]. As the veins surrounding the tumor resembled the crab claws, he named the disease after the Greek word *carcinos*. Cornelus Celsus (ca. 25 B.C.-50 A.D.), who described the first surgeries on cancers, translated Greek carcinos into now commonly used Latin term cancer. . Claudius Galen (129-216 A.D.), the most famous Roman Empire physician, who wrote about 500 medical treatises, left a comprehensive descriptions of many neoplasms. He introduced the Greek word oncos (swelling) to describe tumors. Nowadays the use of Hippocrates and Celsus term is limited to describe malignant tumors, while Galen's term is used as a part of the name of the branch of medicine that deals with cancer - that is oncology. In 1985, Carol Greider isolated the enzyme telomerase, controlling the elongation of telomeres. Four years later, in 1989, Gregg B. Morin reported the presence of telomerase in human tumor cells and linked its activity with the immortality of these cells (inability to apoptosis), while Greider discovered the lack of active telomerase in normal somatic cells apart from stem cells, keratinocytes, intestines, and hair follicle. It was discovered that deactivation of telomerase prompts the apoptosis of human breast and prostate cancer cells. These results indicated the important role of telomerase in the process of oncogenesis.

Cells can die by two different ways: necrosis and apoptosis. Necrosis is caused by outside damage, recognized by destruction of plasma membrane and intracellular organelles and molecules. Necrotic cells, when microscopically observed, appear swollen with broken plasma membrane, and release cytoplasmic contents to the neighboring tissue. Necrosis can happen in a few seconds[3].

In apoptosis, biochemical and morphological events are usually organized in a cascade of very specific and controlled steps. The beginning of apoptosis is marked by chromatin condensation that occurs in parallel to the shrinking of the cell. Fragmentation of the nucleus, transformation of the cell surface, and complete splitting of the cell contents to apoptotic bodies attached to the membrane, accompany those changes [4]. One of the important features of apoptosis, in most cell lines, is DNA fragmentation, catalyzed by endogenic endonucleases [5]. Final events of apoptosis include activation of specific cytoplasmic proteases named caspases [3]. In mammalian cells, caspases are activated in a cascade, resulting in inappropriate activation or fast damage to structural proteins, as well as to important signaling processes, homeostasis and repair enzymes [6.] Caspase-3 is essential for a number of morphological and biochemical events associated with apoptosis [7]. The process of apoptosis is slower than necrosis and happens in a few hours or days, depending on the inducer. This kind of death may be regarded as 'cell suicide'[8]. Chemotherapeutic drugs work usually by induction of apoptosis in cancer cells [9]. The drugs which act by inducing apoptosis shows very good therapeutic index.

Increased bcl-2 protein production occurs in several cancers, including B cell leukemia's, lymphomas, colon prostate cancers neuroblastoma and is linked to poor disease outcome which inhibit apoptosis. In addition, overexpression of the bcl-2 gen may confer resistance to chemotherapeutic drugs. Since the discovery of bcl-2 and its role in apoptosis, scientists have determined that this complicated process has many genetic controls. For example, the p53 protein, known as the guardian of the human genome, serves as an important tumor suppressor because it neither blocks the cell division of a genetically damaged cell or triggers apoptosis by causing damage to the mitochondria and cytochrome C released. In 55 to 70 percent of human cancers, however, genetic mutations render the p53 protein deficient and cells with DNA damage can continue to accumulate. Loss of p53 function is associated with tumor aggressiveness and resistance to anticancer treatments.

Mounting evidence indicates that the acquired ability to resist apoptosis is hallmark of most, and perhaps all types of cancer. As scientist learns more about how apoptosis is thwarted by cancer, they are also gaining a greater understanding of why many tumors are resistant to the cell suicide inducing effects of radiation and chemotherapy. Researchers are exploring how apoptosis is regulated, how it might be repaired through genetic therapies, and how it can be selectively triggered, through tailored treatments, to induce suicide in cancer cells while leaving healthy cells alone.

Apoptosis

Cell death plays a crucially important role in animal and plant development, and it usually continues into adulthood. The 'normal' cell deaths are suicides, in which the cells activate an intracellular death program and kill themselves in a controlled way- a process known as programmed cell death which occurs by apoptosis.

Cells dying by apoptosis undergo characteristic morphological changes. They shrink and condense, the cytoskeleton collapses, the nuclear envelope disassembles and the nuclear chromatin condenses and breaks up into fragments. The cell surface often blebs and if the cell is large, often breaks up into membrane- enclose fragments called apoptotic bodies. Most importantly, the surface of the cell/ apoptotic bodies becomes chemically altered, so that a neighbouring cell or a macrophage rapidly engulfs them before they can spill their contents. In this way the cells die neatly and are rapidly cleared away.

The induction of apoptosis involves different signals depending on different cell types. These signals engage unique signaling pathways, but in all cases, the actual execution of the cell involves the activation of a specialized set of proteases known as caspases. The activated caspases in turn activates other effecter caspases. This catalytic cascade culminates in cell death. The programmed cell death occurs mainly by two pathways:

- Extrinsic Pathway
- Intrinsic Pathway (Mitochondrial Death receptor Pathway)

Medicinal Plants

Traditional medicine is a practice that has been carried out from antiquity to our present time by inhabitants of the indigenous pueblos among population. In the traditional Ayurveda medicine, plants are of great importance, which can be considered as evidence of their effectiveness for the control of many types of diseases. Likewise, they comprise one of the most important alternatives for health care, above all, in communities where primary health services are not accessible. In addition, they can be taken advantage of widely as a natural renewable resource. Together with what was previously described, the traditional medicine of the indigenous pueblos was recognized by the World Health Organization (WHO), which caused a powerful drive toward the research of medicinal plants [10].

Now days the Traditional Medicines and plants are the reference of knowledge, application and new ideas for novel treatments and drug designing. The University of Wisconsin, for instance lists 150 plants which they have established as having potential value in the treatment of cancer. Ongoing research is being done throughout the world to seek out effective treatments for cancer,

including the use of plants to relieve and treat cancer patients. An alternative to chemotherapy, which is the most common means by which doctors and specialists treat cancer, organically based treatments may not have the severe side effects that radial treatments and chemotherapy has. One motivating factor to finding alternative methods is the harsh side effects of cancer treatments. The use of plants when treating cancer patients is considered a natural alternative, because some plants may contain properties that naturally have the ability to prevent the spread or risk of developing various forms of cancer. As in all medical testing, careful precautions and considerations are taken when studying the different compounds present in plants that are known to treat cancer.

Bonellia albiflora

The hexanic fraction of B. albiflora roots exerts cytotoxic effects and induces apoptosis via the extrinsic pathway, which suggests its potential for the treatment of cancer. The complete isolation of the components present in the hexane fraction of B. albiflora for evaluation in the cytotoxic assay and induction of apoptosis, to elucidate which are the active compounds as well as to understand the mechanism of action [2.]

Toona sinensis

The chemical constituents from Toona sinensis, and their biological activities have assumed significance for the rational development and utilization of this plant. The constituents which were isolated from Toona sinensis shows tumor cell growth inhibition effects of the BTA and OEA and showed potent activities on MGC-803 and PC3 cell lines in a dose dependent manner. The IC_{50} values of BTA and OEA on MGC-803 and PC3 cells were determined to be 17.7 μM and 13.6 μM, 26.5 μM and 21.9 μM, respectively, all of which were lower than that on NIH3T3 cells (IC_{50} > 50 μM). In addition, the apoptosis ratios induced by BTA and OEA caused apoptosis of MGC-803 cells were quantitatively assessed by flow cytometry, with apoptosis ratios of 27.3% and 24.5% after 72 h of treatment at 20 μM, respectively. Interestingly, the BTA and OEA induced cell apoptosis through the mitochondrial pathway in MGC-803 cells. These findings have implied that BTA and OEA has potential therapeutic value for treatment of cancer [29].

Plant stress hormones

Sodium salicylate (SA) induces apoptosis in cell lines of human myeloid leukemia, through activation of caspase-3,[11] and in FS-4 fibroblasts [12]. SA can also inhibit growth of breast cancer cells [13]. SA is a plant stress hormone and a central mediator of plant defense responses to pathogens. Two other plant stress hormones: jasmonic acid (JA, Figure 1) and methyl jasmonate (MJ, Figure 1), belong to the group of natural bioregulators named *jasmonates* [14]. JA is crucial to intracellular signals in response to injury and MJ causes the induction of a proteinase inhibitor,

which is accumulated in response to wounding or pathogenic attacks, at very low concentrations[15]. The plant stress hormones SA, JA and MJ cause suppression of proliferation and death in various cancer cell lines, without affecting normal lymphocytes. In addition, MJ was shown to increase significantly the survival of lymphoma-bearing mice. These results suggest that plant stress hormones may share a cytotoxic potential towards cancer cells [15]. A coordinated activation of programmed cell death (PCD) and defense mechanisms often accompany the antimicrobial response of plants and animals [16]. In plants, this response is termed the hypersensitive response (HR) and results in the formation of a zone of dead cells around the infection site, the synthesis of SA, and accumulation of antimicrobial agents, such as pathogenesis-related proteins and phytoalexins [17]. The layers of dead cells that surround the site of pathogen entry are thought to function as a physical barrier that inhibits further proliferation and spread of the pathogen [18]. Because the plant stress hormone SA induces in mammalian cells intracellular biochemical events typical of stress response [12,19] and apoptosis [11].

Plant-Derived Polyphenolic Compounds.

Among the various pharmacological properties of plant derived polyphenolic antioxidants is their action as preventive agents against cancer [20]. This is generally considered to react their ability to scavenge endogenously generated oxygen radicals or those radicals formed by various xenobiotics, radiation, and so forth. These compounds are themselves capable of oxidative DNA cleavage, particularly in the presence of transition metal ions such as copper [21]. Polyphenols such as tannins have great reducing power and are known to form complexes with various metal ions [22]. Accordingly, as with OP, polyphenols also are conceivably capable of mobilizing and redox-cycling endogenous copper ions, both from chromatin and from copper-binding proteins, especially ceruloplasmin. Some evidence suggests that polyphenolic compounds such as tannins and resveratrol are able to traverse cell membranes and may enter the cytoplasmic or nuclear space. Resveratrol is suffciently hydrophobic and has been shown to be present in such tissues as heart, liver, and kidney [23]. A model for the entry and Interaction of polyphenols with chromatin-associated copper has been described [24]. The ability of gallo tannins to enter the cell is indicated by the observation that tannic acid prevents formation of the benzo[*a*]-pyrene-DNA adduct by inhibiting the binding of the ultimate carcinogen to target tissue DNA rather than by altering the metabolism of benzo[*a*]-pyrene[25,26]. The various anticancer effects and apoptotic DNA fragmentation activities of several plant-derived polyphenols may be explained by their ability to mobilize endogenous or otherwise increased concentrations of copper in cancer cells. Further, the fact that these polyphenolic compounds are ingested by human populations as part of the normal

diet in relatively high concentrations without adverse reactions points to their great potential as putative chemopreventive or therapeutic agents [27].

Diosgenin (a Plant Steroid)

Diosgenin, a plant steroid causes an inhibition of the growth of fibroblast-like synoviocytes from human rheumatoid arthritis, with apoptosis induction associated with cyclooxygenase-2 (COX2) up-regulation. Celecoxib, a selective COX-2 inhibitor, provoked a large decrease in diosgenin-induced apoptosis even in the presence of exogenous prostaglandin E2, whereas interleukin-1β, a COX-2 inducer, strongly increased diosgenin-induced apoptosis of these synoviocytes. Proapoptotic effect of diosgenin is associated with overexpression of COX-2 correlated with overproduction of endogenous prostaglandin E2 and loss of mitochondrial membrane potential, caspase-3 activation, and DNA fragmentation after diosgenin treatment. Although the excess endogenous production of PGE2 appears to be associated with the induction of RA FLS death, the exact mechanism by which this compound brings about this phenomenon remains to be elucidated[28].

CONCLUSION

We have different traditional systems and belief on the basis of cultural origin, philosophies and civilizations. Most of our Traditional medicines were remain mainly localized in their own country. But nowadays theAyurvedic traditional medicines are increasingly used in many parts all over the world, the origin of all these medicines are our Mother Nature and plants. Plants are abound of compounds having chemo protective or anti-cancer activities, we should have to exploit them for the development of new anti-cancer drugs. In this review some examples of plants with of foreign and naturalorigin that possess anti-cancer activity by inducing apoptosis are have been presented. These plants possess good anti-cancer activity induces apoptosis which suggests its potential for the treatment of cancer. So we can exploit them and design new drugs with least side effects.

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REFERENCE

1. Ames, B. N., Gold, L. S., and Willett, W. C. The causes and prevention of cancer. *Proc.* Natl. Acad. Sci. U.S.A. 1995; 92: 5258–5265.
2. Arends J, Moris G, Wyllie AH. Apoptosis: the role of the endonuclease. Am J Pathol.

1990; 136: 593–608.

3. Bailly JD, Skladanowski A, Bettaieb A, Mansat V, et al. Natural resistance of acute myeloid leukemia cells lines to mitoxantrone is associated with lack of apoptosis. Leukemia. 1997; 11: 1523–1532.
4. Bertelli, A. A., Giovannini, L., Stradi, R., Berte et al. Plasma, urine and tissue levels of Tran- and *cis*-resveratrol (3, 40,5trihydroxystilbene) after short-termorprolonged administration of red wine to rats. Int. J. Tissue React.1996; 18: 67–71.
5. Bertrand.L, Pascale V.S, Cecile.C, et al .Diosgenin, a Plant Steroid, Induces Apoptosis in HumanRheumatoid Arthritis Synoviocytes With Cyclooxygenase-2 Over expression .Arthritis Res Ther. 2004; 6: 4.
6. Butler M.S. The role of natural product chemistry in drug discovery. Journal of Natural Products. 2004; 67: 2141-2153.
7. Dangl JL, Dietrich RA, Richberg MH. Death don't have no mercy: cell death programs in plant–microbe interactions. Plant Cell.1996; 8: 1793–1807.
8. Das, M., Mukhtar, H., Bik, D. P., and Bickers, D. R. Inhibition of epidermal xenobiotic metabolism in SENCAR mice by naturally occurring plant phenols. Cancer Res. 1987; 47: 760–766.
9. Demain AL, Vaishnav P. Natural products for cancer chemotherapy. Microb Biotechnol. 2011; 4: 687–699.
10. Farmer EE, Ryan CA. Interplant communication: air-borne methyl jasmonate induces synthesis of proteinase inhibitors in plant leaves. Proc Natl Acad Sci USA. 1990; 87: 7713–7716.
11. Fujita J. Cold shock response in mammalian cells. J Mol Microbiol Biotechnol.1999; 1: 243–255.
12. Goodman RN, Novacky AJ. The hypersensitive response reaction in plants to pathogens: a resistance phenomenon. American Phytopathological Society: St Paul, MN (Abstr).1994.
13. Hemingway, R. W., and Karchesy, J. J. Chemistry and Significance of Condensed Tannins.Plenum. New York. 1989.
14. Hadi S. M., Asad S. F., Saurabh Singh, and Aamir Ahmad.Hypothesis PaperPutative Mechanism for Anticancer and Apoptosis-Inducing Properties of Plant-Derived Polyphenolic Compounds.
15. Klampfer L, Cammenga J, Wisniewski HG, Nimer SD. Sodium salicylate activates caspases and induces apoptosis of myeloid leukemia cell lines. Blood.1999;93: 2386–2394.

16. Li, Y., and Trush, M. A. Reactive oxygen dependent DNA damage resulting from the oxidation of phenolic compounds by a copper-redox cycle mechanism. Cancer Res. 1994; 54: 18955–18985.
17. Massaoka MH, Matsuo AL, Figueiredo CR, Farias CF, Girola N. Jacaranone induces apoptosis in melanoma cells via ROS-mediated down regulation of Akt and p38 MAPK activation and displays antitumor activity in vivo. PLOS One. 2012; 7: 1–11.
18. Mitler R, Lam E. Sacrifice in the face of foes: pathogen-induced programmed cell death in higher plants. Trends Microbiol .1996; 4: 10–15.
19. Mukhtar. H, Das M, Khan W. A., Wang, Z. Y. et al Exceptional activity of tannic acid among naturally occurring plant phenols in protecting against 7,12-dimethyl benz(a)anthracene-, benzo(a)pyrene-, 3-methyl cholanthrene- and N-methyl-N-nitrosourea–induced skin tumorigenesis in mice. Cancer Res. 1988; 48: 2361–2365.
20. Nicholson DW, Thomberry A. Caspases: killer proteases. Trends Biochem Sci.1997; 22:299–306.
21. Patel B, Sattwik das, Prakash R, Yasir M. Natural bioactive compound with anticancer potential. Int J Adv Pharm Sci. 2010; 1: 32–41.
22. Porter AG, Janicke RU. Emerging roles of caspases-3 in apoptosis. Cell Death Differ.1999; 6: 99–104.
23. Rahman, A., Shahabuddin, Hadi, S. M., Parish, J. H. et al. Strand scission in DNA induced by quercetin and Cu (II): role of Cu (I) and oxygen free radicals. Carcinogenesis. 1989; 10: 1833–1839.
24. Rosa Moo-P, Juan Chale-D and Edgar Caamal-Fuentes. Bonellia albiflora: A Mayan Medicinal Plant That Induces Apoptosis in Cancer Cells. Evidence-Based Complementary and Alternative Medicine. 2013, 8;234-538
25. Schwenger P, Alpert D, Skolnik EY, Vilc˘ek J. Cell-type-specific activation of c-Jun N-terminal kinase by salicylates. J Cell Physiol.1999; 179: 109–114.
26. Schwenger P, Bellosta P, Vietor I, et al. Sodium salicylate induces apoptosis via p38 mitogen-activated protein kinase but inhibits tumor necrosis factor-induced c-Jun Nterminal kinase/stress-activated protein kinase activation. Proc Natl Acad Sci USA. 1997; 94: 2869–2873.
27. Sembdner G, Parthier B. The biochemistry and the physiological and molecular actions of jasmonates. Annu Rev Physiol Plant Mol Biol. 1993; 44: 569–589.
28. Shengjie .Y, Qi Zhao, Hongmei .X, Minjie .L, at al. Antiproliferative activity and

apoptosis-inducing mechanism of constituents from Toona sinensis on human cancer cells. Cancer cell international. 2013.

29. Spieler J. M., "World Health Organization, the special programme of research, development and research training in human reproduction task force on indigenous plants for fertility regulation." Korean Journal of Pharmacognosy.1981; 12: 94– 97.
30. Sotiriou C, Lacroix M, Lagneaux L, Berchem G, Body JJ. The aspirin metabolite salicylate inhibits breast cancer cells growth and their synthesis of the osteolytic cytokines interleukins-6 and -11. Anticancer Res. 1999; 19: 2997–3006.
31. Stewart BW. Mechanisms of apoptosis: integration of genetic, biochemical, and cellular indicators. J Cancer Inst.1994; 86:1286– 1295.
32. Willingham MC. Cyto chemical methods for the detection of apoptosis. J Histochem Cytochem.1999; 47: 1101–1109.
33. Yarbro H, Good M., Frogge M.H. Cancer Nursing Principles and Practice. Boston, Jones & Bartlett Publishers.1879; 6.