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Phytohormones as Potential Anticancer Agents

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ABSTRACT

The global burden of cancer is projected to have more than doubled over the next two decades, raising the prospect of a significant investment in health systems, thus posing a real medical problem. The increasing number of people with cancer highlights the need for more cancer prevention efforts. An established history exists for plant-derived compounds as effective anticancer agents. More recently, several phytohormones have been assessed for their ability to inhibit the growth and survival of human cancer cell lines. Phytohormones or plant hormones are chemical messengers responsible for harmonizing various cellular activities that revolves around growth, development, and stress-response. The aim of this literature review article is to present the current state of knowledge concerning the several naturally occurring phytohormones which have shown enormous potential in the prevention and treatment of variety of different type of cancers.

Keywords- Cancer; Anticancer agents; Phytohormones; Cancer cell lines; Plant hormones

I. INTRODUCTION

Plant hormones (also known as phytohormones) are signal molecules produced within plants, that occur in extremely low concentrations. Plant hormones control all aspects of growth and development, from embryogenesis, the regulation of organ size, pathogen defence, stress tolerance and reproductive development. The term 'phytohormone' was coined by Went and Thimann and used in the title of their book in 1937.

Plant hormones aren't nutrients, but chemicals that in small amounts promote and influence the expansion, development, and differentiation of cells and tissues. The biosynthesis of plant hormones within plant tissues is usually diffused and not always localized. Plants lack glands to supply and store hormones, because, unlike animals—which have two circulatory systems (lymphatic and cardiovascular powered by a heart that moves fluids round the body—plants use more passive means to manoeuvre chemicals around their bodies. Plants utilize simple chemicals as hormones, which move more easily through their tissues. They are often produced and used on an area basis within the plant body. Plant cells produce hormones that affect even different regions of the cell producing the hormone.

II. ROLE OF PHYTOHORMONES IN PLANTS

Different hormones can be sorted into different classes, depending on their chemical structures. Within each class of hormone, the exact structures vary, but they have similar physiological effects.

Auxins

Auxins are compounds that positively influence cell enlargement, bud formation and root initiation. They also promote the assembly of other hormones and in conjunction with cytokinins, they control the expansion of stems, roots, and fruits, and convert stems into flowers [1]. Auxins were the first class of growth regulators discovered [2]. They affect cell elongation by changing cell wall plasticity. They stimulate cambium, a subtype of meristem cells, to divide and in stems cause secondary xylem to differentiate. Auxins act to inhibit the growth of buds lower down the stems (apical dominance), and to promote lateral and adventitious root development and growth. Leaf abscission is initiated by the growing point of a plant ceasing to supply auxins. Auxins in seeds regulate specific protein synthesis,[3] as they develop within the flower after pollination, causing the flower to develop a fruit to contain the developing seeds. Auxins are toxic to plants in large concentrations; they are most toxic to dicots and fewer so to monocots. Because of this property, synthetic auxin herbicides including 2,4-D(2,4-dichlorophenoxyacetic) and 2,4,5- T are developed and used for weed control. Auxins, especially 1-Naphthaleneacetic acid (NAA) and Indole-3-butyric acid (IBA), also are commonly applied to stimulate root growth when taking cuttings of plants. The most common auxin found in plants is indole-3-acetic acid or IAA.

Cytokinins

Cytokinins or CKs are a set of chemicals that influence cellular division and shoot formation. They were called kinins in the past when the first cytokinins were isolated from yeast cells. They also help delay senescence of tissues, are liable for mediating auxin transport throughout the plant, and affect internodal length and leaf growth. Cytokinins and auxins often work together, and therefore the ratios of those two groups of plant hormones affect most major growth periods during a plant's lifetime. Cytokinins counter the apical dominance induced by auxins; they in conjunction

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with ethylene promote abscission of leaves, flower parts, and fruits [4].

Gibberellins

Gibberellins (GAs) comprises of large range of chemicals that are produced naturally within plants and by fungi. They were first discovered when Japanese researchers, including Eiichi Kurosawa, noticed a chemical produced by a fungus called *Gibberella fujikuroi* that produced unusual growth in rice plants [5]. Later it was discovered that GAs are also produced by the plants themselves and they control numerous facets of development across the life cycle. The synthesis of GA is fully upregulated in seeds at germination and its presence is essential for germination to occur. In seedlings and adults, GAs strongly encourage cell elongation. GAs also encourage the transition between vegetative and reproductive growth and are also required for pollen function during fertilization [6].

Abscisic acid

Abscisic acid (also known as ABA) is one of the foremost vital plant growth regulators. It was discovered and researched underneath two totally different names before its chemical properties were absolutely famed, it was known as dormin and abscicin II. Once it was known that the two compounds are identical, it was named abscisic acid. The name "abscisic acid" was given as a result because of its presence in high concentrations in freshly abscised or freshly fallen leaves.

It acts as an inhibitory chemical compound that affects bud growth, and seed and bud dormancy. It mediates changes in the apical meristem, inflicting bud dormancy and therefore the alteration of the last set of leaves into protecting bud covers. In plant species from temperate section of the world, it plays a task in leaf and seed dormancy by inhibiting growth, but, because it is dissipated from seeds or buds, growth begins. In different plants, as ABA levels decrease, growth then commences as gibberellin levels increase. Without ABA, buds and seeds would begin to grow throughout warm periods in winter and be killed once it froze again. Since ABA dissipates slowly from the tissues and its effects take time to be offset by different plant hormones, there is a delay in physiological pathways that offer some protection from premature growth. It accumulates among seeds throughout fruit maturation, preventing seed germination among the fruit, or seed germination before winter. Abscisic acid's effects are degraded among plant tissues throughout cold temperatures or by its removal by water washing in out of the tissues, absolving the seeds and buds from dormancy [7].

Jasmonates

Jasmonates (JAs) are lipid-based hormones that were initially segregated from jasmine oil [8]. JAs are particularly vital within the plant response to attack from herbivores and necrotrophic pathogens [9]. The foremost active JA in plants is jasmonic acid. Jasmonic acid are often metabolized into methyl-JA, that is a volatile chemical compound. This uncommon property means methyl-JA will act as an airborne signal to commune herbivore attack to alternative distant leaves within one plant and as an indication to adjacent plants [10]. Additionally, to their role in defence, JAs are believed to play roles in seed germination, the storage of protein in seeds and root growth [9].

Strigolactones

Strigolactones (SLs) were initially recognised via studies into the germination of the parasitic weed *Striga lutea*. It was found that the germination of *Strigaspecies* was stimulated by the presence of a compound exuded by the roots of its host plant [11]. It was later shown that SLs that are exuded into the soil promote the growth of symbiotic arbuscular mycorrhizal (AM) fungi. Recently, another role of SLs was diagnosed in the inhibition of shoot branching [12]. This discovery of the role of SLs in shoot branching led to a dramatic increase in the interest in these hormones, and it has since been shown that SLs play important roles in leaf senescence, phosphate starvation response, salt tolerance and light signalling [13].

Brassinosteroids

Brassinosteroids are a type of polyhydroxysteroids, the unique example of steroid based hormones in plants. Brassinosteroids regulate cell elongation and division, gravitropism, resistance to stress, and xylem differentiation. They inhibit root growth and leaf abscission. Brassinolide was the first identified brassinosteroid and was isolated from extracts of rapeseed (*Brassica napus*) pollen in 1979 [14].

III. PHYTOHORMONES AS POTENTIAL ANTICANCER AGENTS

Auxin – (Indole 3 Acetic Acid)

Indole-3-acetic acid (IAA), the major form of a plant growth hormone in higher plants (auxin), is a heterocyclic compound known to regulate cell division, elongation, and differentiation [15, 16]. Reactive oxygen species (ROS), the products of a reaction between IAA and extracellular peroxidase, have been reported to play a role in cell elongation of plants [17]. Currently, this ROS-producing reaction of IAA with peroxidase is emerging as a novel anticancer therapy. It has been suggested that IAA has merit as a potential pro-drug for cancer therapy in combination with horseradish peroxidase (HRP) [18].

Application of the IAA/HRP system to cancer therapy is suggested in various ways, such as antibody-directed enzyme/ pro-drug therapy, gene-directed enzyme/pro-drug therapy, or polymer-directed enzyme/pro-drug therapy [18,19,21]. It has been reported that IAA can generate free radicals in combination with UVB. The cytotoxic actions on several cancer cells, such as hepatomas and melanomas were also demonstrated [20, 21, 22].

A reported study determined the effects of IAA in combination with UVB in PC-3 cells and examined the possible application as a new PDT for prostate cancer. It was confirmed that IAA at 500 μM produced free radicals when irradiated by 100 mJ/cm2 of UVB. UVB-activated IAA (IAA^{UVB}) induces cell death of PC-3 cells. This study also examined the effects of IAA^{UVB} on the phosphorylation of JNK and p38 MAPK in PC-3 cells. It was found that only IAA^{UVB} induced JNK and p38 MAPK phosphorylation, whereas IAA or UVB alone-treated groups failed to activate JNK and p38 MAPK. It was demonstrated IAA^{UVB}-induced apoptosis by flow cytometric analysis. The apoptosis was significantly enhanced in IAA^{UVB}-treated PC-3 cells, but not in the IAA or UVB group. Taken together, the data of this study demonstrated that non-cytotoxic IAA induced cell death in combination with UVB irradiation by increasing apoptosis in PC-3 cells [23].

In another study, human pancreatic cancer BXPC-3 cells were selected to evaluate IAA/HRP, which could be used in treatment of human pancreatic cancer. In this study, the MTT assay showed that the viability of BXPC-3 cells decreased with increase of IAA in the presence of HRP. In addition, TUNEL analysis showed that IAA/HRP induced apoptosis of BXPC-3 cells [24].

Cytokinins

Cytokinins are important purine derivatives that act as hormones to control many processes in plants [25]. Naturally occurring cytokinins are mainly adenine derivatives such as isopentenyladenine (IPA) and trans-zeatin, while synthetic cytokinins also include several adenine analogues, such as kinetin and 6-benzyladenine [26].

Recent study showed that cytokinins effectively inhibit the proliferation and induce the granulocytic differentiation of human myeloid leukemia HL-60 cells [27]. The metabolism of cytokinins to their nucleotides was closely associated with cytokinin-induced differentiation and growth inhibition. When the cells were incubated with [14C]-benzyladenine, radioactivity was significantly incorporated into RNA and DNA. However, the radioactive nucleotides in RNA or DNA were adenine nucleotides, not benzyladenine nucleotides, suggesting that cytokinins were not incorporated into RNA and DNA. The benzyladenine nucleotides were not stably released into the medium in intact form. Cytokinins effectively induced a phosphorylated (active) form of mitogen-activated protein kinase (MAPK). MAPK activation was necessary for cytokinin-induced differentiation, because PD98059, an inhibitor of MAPK kinase, suppressed the differentiation induced by cytokinins. These results suggest that cytokinin nucleotides themselves play an important role in inducing the differentiation of HL-60 cells [28].

Gibberellins

GA-13315 is a novel synthetic gibberellin derivative, and possesses potent antitumor activity due to the existence of an α,β-unsaturated ketone moiety [29]. GA-13315 demonstrates inhibitory effect on proliferation of A549 cells in xenograft mice models [30]. In addition, more recent evidence revealed that GA-13315 inhibited the growth and proliferation of oral, breast, and leukemia tumor cells through exerting antiangiogenic activity [30, 31]

Xie et al. [32] reported that GA-13315 exhibited potent, dose- and time dependent anti-proliferative activity, and the IC50 values were 37.43 ± 2.73, 28.08 ± 7. 76 and 19.29 ± 7.61 μM at 24, 48, and 72 h, respectively. Their xenograft experiment revealed that tumor weight and volume were significantly decreased after GA-13315 3 mg/kg and 9 mg/kg ($P < 0.05$) treatment, and GA-13315 had low toxicity in bone marrow, kidney, and colon tissues. GA-13315 triggered remarkable apoptosis in A549 cells at the concentration of 25.6 μM and 32 μM ($P < 0.05$) and activated caspase-3, − 8 and − 9. Moreover, GA-13315 induced apoptosis through the mitochondrial apoptosis pathway by elevating the Bax/Bcl-2 ratio, releasing cytochrome c and activating caspase-9 in A549 cells. In the endoplasmic reticulum apoptosis pathway, the levels of caspase 4, ATF4, GRP78 and GADD153 were markedly upregulated.

Abscisic Acid

Abscisic acid (ABA) is an important phytohormone that regulates plant growth, development, dormancy, and stress responses. Recently, it was discovered that ABA not only exists and functions in plants, algae, cyanobacteria, and fungi, but is also present in a wide range of lower animals, such as sponges [33,34], as well as higher mammals [35]. ABA stimulates the stress response (heat and light) in animal cells, immune responses in leukocytes, insulin release from pancreatic b cells, and the expansion of mesenchymal and colon stem cells. ABA also inhibits the growth and induces the differentiation of cancer cells.

ABA was reported as an anti-cancer compound in a US patent issued to Dr. Virginia Livingston in 1976 [36]. The inventor reported that ABA ‘‘neutralized’’ the human chorionic gonadotropin (hCG), which is a negatively charged glycoprotein that reportedly coated cancer cells and prevented immune cells (the outer membranes are normally negatively charged) from getting close to attack the cancer cells, thereby facilitating anticancer immune responses. Tan et al. [37] reported in a China patent that ABA effectively inhibits the proliferation of tumor cells; stagnates the cells in S phase, stops cell division, and induces differentiation of tumor cells or reverts cancerous cells to normal cells. They also reported that ABA induces apoptosis and inhibits angiogenesis in a variety of cancer cells.

Because calcium signaling is a key regulator of apoptosis, changes in calcium distribution in the cell activate cellular cascades, which lead to cell death [38]. The calcium signaling pathway activated by ABA is like the pathway activated by certain types of chemotherapeutic agents used in cancer treatment, such as staurosporine, doxorubicin, tamoxifen, and etoposide. These drugs function by increasing oxidative stress and apoptosis rates in cancer cells, both of which are mediated by increasing [Ca^{2+}] [39].

Jasmonates – (Methyl Jasmonates)

Methyl jasmonate (MeJa) is a lipid-derived endogenous hormone that plays crucial roles in both developmental processes and diverse defence responses in plants. Recently it was discovered that plant stress hormones called jasmonates, possess anticancer activities in vitro and in vivo [40, 41]. Jasmonates were found to suppress proliferation and induce cell death in various cancer types, including breast cancer, prostate cancer, melanoma, neuroblastoma, lymphoblastic leukaemia and lymphoma.

Fingrut and Flescher have reported in 2002 that MeJa can induce apoptosis in human cancer cells, including Molt-4, SK-28, LNCaP, and MCF7. They also demonstrated that MeJa is in contrast to another plant hormone, salicylic acid (SA), in terms of their effect on cancer cells, as the latter arrests the cell cycle and suppresses cell proliferation in each of the cell lines mentioned above. They further showed that after treatment with MeJa, mice bearing EL-4 lymphoma can survive for significantly longer periods of time than untreated mice [42].

Three potential mechanisms of action have been proposed to explain the anticancer activity of jasmonates. First, the bioenergetics mechanism that involves severe depletion of ATP via mitochondrial perturbation, second, the induction of re-differentiation via mitogen-activated protein kinase (MAPK) activity and third, through apoptosis induction via the generation of reactive oxygen species (ROS) and elevation of the proapoptotic Bcl-2 proteins ([40, 41])

Milrot et al. [43] further investigated the mode of action of methyl jasmonate in cervical cancer cells, explored the effect of MJ on HPV E6 and E7 gene expression and established the effects of E6 and E7 on the response to MJ. Their study showed that in addition to the short-term effect of MJ on cervical cancer cell viability, MJ effectively reduced the survival of cervical cancer cells as determined in clonogenicity assays. MJ induced apoptosis in cervical cancer that was indicated by caspase 3-activation and PARP cleavage. Formation of mitochondrial superoxide anion was detected in part of the cancer cells lines, however down regulation of survivin, a major inhibitor of caspase-3 activation and apoptosis execution, was identified in all cervical cancer cells. MJ did not reduce the mRNA levels of HPV E6 and E7, though it significantly reduced the levels of the E6 and E7 proteins.

Strigolactones

Strigolactones (SLs) are a novel class of plant hormones produced in roots and regulate new above ground shoot branching, by inhibiting self-renewal of undifferentiated meristem cells. It is shown that SLs cause meristem cell cycle arrest and atrophy mainly by inhibiting cyclin B transcription [44]. Currently, more than 10 natural SLs exist and several synthetic analogues have been synthesized and used in various studies [45–47].

Pollock et al. [48] investigated the effects of six synthetic SL analogues on breast cancer cell lines growth and survival. It was shown that SL analogues were able to inhibit proliferation and induce apoptosis of breast cancer cells but to a much lesser extent ‘‘non-cancer’’ lines. Given the therapeutic problem of cancer recurrence which is hypothesized to be due to drug resistant cancer stem cells, they also tested the ability of SL analogues to inhibit the growth of mammosphere cultures that are typically enriched with cancer stem-like cells. They show that SLs are potent inhibitors of self-renewal and survival of breast cancer cell lines grown as mammospheres and even a short exposure lead to irreversible effects on mammosphere dissociation and cell death. SL analogues inhibited hormone responsive and hormone independent breast cancer cell lines. Immunoblot analysis revealed that SLs analogues induce activation of the stress response mediated by both P38 and JNK1/2 MAPK modules and inhibits PI3K/AKT activation. Taken together, this study indicates that SLs may be promising anticancer agents whose mechanism of action may involve stress and survival signaling modulation.

Brassinosteroids

Brassinosteroids (BRs) are plant steroids which regulate a number of plant processes including growth, differentiation, senescence, and disease resistance. BRs have been isolated from seeds, fruits, leaves, galls, and pollen. In cancer cell lines, BRs regulate cyclin D1 and cyclin-E levels causing G1 arrest and apoptosis [49, 50].

It is discovered that some natural BRs can inhibit the growth of several cancer cell lines at micromolar concentrations. Natural BRs can induce cell growth inhibitory responses, arrest cells in the G1 phase of the cell cycle and induce apoptosis in both hormone-sensitive and -insensitive breast cancer cell lines [51].

Steigerova et al. demonstrated several effects of natural cytotoxic BRs and provided indications of the molecular mechanisms that may be involved. The studied BRs [28-homocastasterone (28-homoCS) and 24-epibrassinolide (24-epiBL)] could cause cell cycle arrest and some apoptotic changes in the investigated breast cancer cell lines [MCF-7 and MDA-MB-468]. A major finding was that BRs can cause cell cycle blockade and apoptosis of hormone-sensitive and -insensitive human breast cancer cells. This finding is important, since breast cancer progresses from an estrogen-responsive to a late estrogen-insensitive

(metastatic) form, and at the time of clinical diagnosis, most breast cancers include a mixture of estrogen-sensitive and -insensitive cells. Therefore, eliminating both carcinoma cell types may be crucial for effective control of breast cancer. Down-regulation of the ERs following BR treatment was also reported. In addition, BR application to breast cancer cells resulted in G1 phase arrest [50]. These results suggest that BRs and their analogues could play valuable therapeutic roles.

IV. CONCLUSION

For millennia, the natural products have been used by man as a remedy in traditional medicine. The increasing number of people with cancer highlights the need for more cancer prevention efforts. Recent research has shown that natural substances are able to prevent the development of many cancers. In experimental studies, it has been found that phytohormones have anticancer capabilities. Some phytohormones affects each phase of carcinogenesis by modulating signal transduction pathway in cells that control cell growth & division, apoptosis, angiogenesis & metastasis. A list of phytohormones directly inhibit angiogenesis. Therefore, phytohormones have therapeutic potential.

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