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Cell growth inhibition by applying abscissic acid (ABA) Hormones

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Abstract
The review study was carried out from different research data to find out the innovative latest information on cell growth inhibition using abscissic acid (ABA) hormone in plant and animal. From the review study results, ABA hormones in defined concentration of treatment effective for growth inhibition of cell. In addition, the effects of ABA on nutrient uptake in Plant, animal and human cell, cancer cell inhibition, physiological relationship of ABA with mammalians, ABA uses as new drug, Na+ mechanisms in cells and cancer cells, apoptosis by ABA action, ABA acts in immune system, ABA Against Human Stress, ABA G-protein signaling pathway and ABA application in pharmaceutical medicine were noted from different review data.

Keywords: aba, cell inhibition, growth, protein, drug

1. Introduction
Abscisic acid (ABA) hormone is well known as a plant hormone. ABA functions in many plant developmental processes, including bud dormancy. It is degraded by the enzyme abscisic acid 8'-hydroxylase into phaseic acid. Abscisic acid (ABA) is an isoprenoid plant hormone, which is synthesized in the plastidal 2-*C*-methyl-D-erythritol-4-phosphate (MEP) pathway; unlike the structurally related sesquiterpenes, which are formed from the mevalonic acid-derived precursor farnesyl diphosphate (FDP), the C_{15} backbone of ABA is formed after cleavage of C_{40} carotenoids in MEP. Zeaxanthin is the first committed ABA precursor; a series of enzyme-catalyzed epoxidations and isomerizations via violaxanthin, and final cleavage of the C_{40} carotenoid by a dioxygenation reaction yields the proximal ABA precursor, Xanthoxin, which is then further oxidized to ABA. Via abscisic aldehyde (Nambara and Annie, 2005) [17].

1.2. Effects in Plant growth inhibition
Hossain (2014) [12] conducted an experiment to investigate the genetically dwarf of peach tree by growth inhibition hormone like ABA. It is reported that by this study, it is possible to make peach tree greatly dwarfed (small growth tree size) by using ABA 1000 and 2000ppm applied to the bark strips of partially ringed trees. The growth inhibitor (ABA) was used by swabbing method with cotton to the bark band (strip) of 2 years and one year trees surface only. It has been reported that this study had dwarfing effect on vigorous peach trees grafted on vigorous rootstocks. From the figure, externally also we can explain that there might be genetically dwarf peach trees produced and we found all shoot growth reduced 60% at 1000pm and 65% at 2000ppm ABA. Almost same proportion of root growth was reduced in the case of both concentrations of ABA. Furthermore, this genetically modified ABA hormonal method is applicable for all fruit species. He also suggested that there is a good prospect of inhibition of cancer cell by ABA application at different concentration though he observed the positive inhibition result for plant growth (cell and tissue, root and shoot).
ABA is basically response to be involved in abscission. ABA-mediated signaling also plays a significant part in plant responses to environmental stress and plant pathogens (Zhu, 2002) [27]. The plant genes for ABA biosynthesis and sequence of the pathway have been elucidated (Nambara and Annie, 2005) [17]. Abscisic acid owes its names to its role in the abscission of plant leaves. In preparation for winter, ABA is produced in terminal buds. This slows plant growth and directs leaf primordia to develop scales to protect the dormant buds during the cold season. ABA also inhibits the division of cells in the vascular cambium, adjusting to cold conditions in the winter by suspending primary and secondary growth.

1.3. ABA Inhibits Nutrient uptake in Plant
Humble *et al*. (1971) [13] stated that stomatal movements determined that K+ was the specific ion involved, not showing significant importance the rest of the ions. It had been taken relevance, due to that ABA also moved other cations as Ca2+, to be transported inward and anions to be transported outward. ABA also inhibited K+ uptake, which was required to prevent stomatal opening (Schroeder *et al*. 2001) [20]. According to Raschke (1987) and Shimazaki K *et al*. 1986, ABA prevented stomatal opening by rapidly blocking H+ extrusion and K+ influx (Zeevart *et al*. 1988). In root, ABA had a similar effect as it was exerted in leaves when it prevented stomatal opening. In excised barley roots of Hordeum distichon, ABA inhibited accumulation, transported and made uptake of K+ and Na+ to avoid osmotic stress during drought (Behl *et al*. 1979) [2]. Wilmer *et al*. 1969, also demonstrated that Na+ and K+ were important in stomatal mechanisms.

1.4. ABA target cells in plant and animal

It had been discovered that, bits of tissue from almost any part of the plant could be excised and grown in cultures. The new cells were not usually organized as differentiated cells, but they produced a formless mass called callus. In the plant, such cells may have a finite life span and form differentiated cells such as roots and buds, if the appropriate growth hormones are supplied (Galston, 1994). ABA as plant hormone is directly involved in plant cell differentiation. In plants, the ABA target cells are embryonic cells and meristems and differentiated cells as stomas. It has been proved ABA action in inhibition of seed and bud germination, and in control of stomatal closure. It has also been defined that tumors are composed of highly aggressive undifferentiated cells and differentiated as well. Undifferentiated cells are biochemically similar to embryonic cells, because the increased expression of embryonic genes in such cells. Stomas as cancer cells as well accumulate solutes and water. In plants, during the stage of stomatal opening, stomas store mainly K+ and water.however, animal cancer cell accumulates Na+ and water. An apoptotic process makes that, cells suffer a phenomenon of shrinkage, which is a mechanism physiologically similar to the mechanism of ABA stomata closure in plants.

1.5. Physiological relationship of ABA with mammalians

Le page-Degivry *et al*. (1986) reported that ABA presented in the central nervous system of pigs and rats. ABA was identified by using a radioimmunoassay in different tissues demonstrated a bigger amount of ABA found in brains than any of the other tissues. The final product of purification had the same properties as ABA, inhibiting stomatal aperture of abaxial epidermis strips of setcreasea purpurea boom (commelinaceae). They remarked that, the ABA presence can't be considered an ABA containing diet consequence, and suggested metabolic pathways identification for ABA biosynthesis in the brain.

1.6. Effects in Animal and human cell

ABA has also been found to be present in metazoans, from sponges up to mammals including humans (Na-Hang 2011). At present its biosynthesis and biological role in animals is poorly understood. ABA has recently been shown to elicit potent anti-inflammatory and anti-diabetic effects in mouse models of diabetes/obesity, inflammatory bowel disease, atherosclerosis and influenza infection. Many biological effects in animals have been studied using ABA as a nutraceutical or pharmacognostic drug, but ABA is also generated endogenously by some cells (like macrophages) when stimulated. Its anti-cancer properties are, for example, poorly supported at this moment but not completely dismissed. (A1 US application US20060292215 A1, Gonzalo Romero M, "Abscisic acid against cancer, published 2006-12-28). In mammalian cells ABA targets a protein known as lanthionine synthetase C-like 2 (LANCL2), triggering an alternative mechanism of activation of peroxisome proliferator-activated receptor gamma (PPAR gamma). Interestingly, LANCL2 is conserved in plants and was originally suggested to be an ABA receptor also in plants, which was later challenged. Anmeldung E. (2013) [1] explained that a naturally occurring plant hormone had been investigated with potent properties as anti-cancer. He stated that ABA was able to produce a hyperpolarization condition on plasma membrane through a decrease of intracellular Na+ and K+. This phenomenon was produced in cancer cells by mediation of ion channel and activation of the signaling g-protein pathway. ABA made aborting sustained depolarization in malignant tissue that produced a change in the configurational state of cell from damaged to a normal state. In addition to that a positive polarization of hCG outer layer accomplished through a removal of electrons permited immune system cells coming close to cancer cells for destruction.

1.7. ABA inhibits Cancer cell and uses as new drug

This invention was initially started by considering that, plant hormones such as IAA, GA and cytokinins stimulate cellular growth in plants. Conversely, ABA manifests an antagonist effect in plants by producing cellular growth inhibition. ABA was mentioned for the first time in relation to cancer by Livingston (1984) [14] denominated, “Abscisic Acid Tablets and Process”. In this invention, she experimented with ABA in mice proving ABA neutralizing properties of a Microbic Chorionic Gonadotropin, which was similar to the Human Chorionic Gonadotropin (hCG). Naturally occurring cytokinins such as kinetin and zeatin, which intervene in plant cellular division have been promoted and patented in Europe and USA for treatment of human skin aging by an international biopharmaceutical corporation denominated Senetek. These patents have showed and proven that, kinetin is capable of delaying or preventing a host of age-related changes of human skin fibroblasts grown in laboratory culture. Livingston (1984) [14] mentioned that ABA was able to make proliferating tumor cells stagnate in S-phase and stop cell division, become cancer cells in normal cells, produced apoptosis and inhibited angiogenesis in a variety of tumor cells. In addition, on 2006 and re-examining the Livingston-Wheeler contentions, Marianne Ehrhorn Kruse then in the Department of Biochemistry and Molecular Biology of the University of Southern Denmark, elaborated a master thesis titled “The Importance of Abscisic Acid as Possible New Drug in Cancer Treatment and its Role on Human Chorionic Gonadotropin Pathways”. She found, that aba caused a tumor growth reduction, reduced cell proliferation rate, changed cell cycle progression, and produced induction of apoptosis, in four human cancer cell lines (HELA, DU145, HCT 116 AND K562). ABA identification as an endogenous cytokine in human granulocytes and demonstration of ABA presence in human lymphocytes, fibroblasts, mesenchymal stem cells, platelets andmonocytes has significant importance in its role for fighting cancer cells. Aba Metabolism And

1.8. Na+ Mechanisms in Cells and Cancer Cells

Cone (1974) [7] clarified a relation between EPD also called electrical transmembrane potential (Em) and associated ionic concentration differences in mitogenesis control of normal and cancer cells. It has been pointed out that, a cell multiplication or mitosis is stimulated by a cell depolarization. This phenomenon of potential fall is caused by Na+ concentration increase in the cytoplasm. According to Cone (1974) [7] as density of cells increases, a substantial direct cell to cell surface contact begins to develop as well. Hence, a mitotic activity begins to decrease with a corresponding rise in membrane EPD. Likewise, in order to get a quiescent stage, cells increase membrane EPD by decreasing Na+ concentration in cytoplasm. Cone (1974) [7] described that a cancer cell multiplication or mitosis is characterized by a sustained and pronounced cell depolarization in conjunction to an

increase of Na+ concentration in the cytoplasm. This phenomenon of malignant proliferation blocks or negates the effective functioning of the ionic regulatory system resulting in a sustained cell depolarization with associated inability to lower the Na+ concentration to nonmitogenic levels. That cancer cell inability to decrease Na+ would be associated to a reduction of the effective operation of Na+ pump". In cancer cells, Na+—K+ pump ATPase Enzyme is inhibited and it remains as unable to be reactivated. It reduces the entry of K+ and exits of Na+. The secondary system (Na+—H+ exchanger) already mentioned is activated; according to Mahnensmith *et al*. (1985) [19], this alternative secondary system plays also a pathophysiological role in diverse conditions such as cancer, renal acid-base disorders, hypertension and tissue and organ hypertrophy. Herein, it is possible to state that the Na+, - K+ pump ATPase enzyme is associated to the hyperpolarization condition of normal cells and the secondary antiport system is correlated to the depolarization condition of cancer cells.

1.9. Apoptosis by ABA Action

According to Fingrut *et al*. (2002) [11] from the Tel-Aviv University, plant stress hormones as sodium salicylate (SA), jasmonic acid (JA) and methyl jasmonate (MJ) can suppress the proliferation or cause apoptosis in certain mammalian cancer cells (lymphoblastic leukemia, prostate, breast and melanoma human cancer cells). Although SA, JA and MJ rather hold a secondary role as plant inhibitors, this evidence reveals the power of plant stress hormones against cancer. In this invention, ABA has been correlated to a process of cancer cell normalization. Nevertheless and paradoxically, an apoptosis phenomenon is induced by ABA hormonal action as well. It was experimentally confirmed for first time in cancer cells by Tang *et al*. 2006, from the Chengdu Biological Institute Academy of Sciences and by Marianne Ehrhorn Kruse, then at the University of Southern Denmark. In plants and according to Vanyushin *et al* (2004) [22], peroxides, ABA, ethylene releaser ethrel, and DNA methylation inhibitor 5-azacytidine induce and stimulate apoptosis. This research points out distint ultrastructural features of apoptosis such as: compaction, vacuolization and fragmentation of cytoplasm in the apoptotic cell; appearance in the vacuole of unique single-membrane vesicles containing active organelles; cessation of nuclear DNA synthesis, and, condensation and margination of chromatin in the nucleus; internucleosomal fragmentation of nuclear DNA; and intensive synthesis of mitochondrial DNA in vacuolar vesicles.

1.10. ABA acts in Immune System

ABA K+ and Na+ efflux from cell is a common phenomenon during ABA cell normalization and apoptosis. ABA cell normalization produces that, those ions "temporarily" remain outside of cell. Under that mechanism, K+ and water return to the cancer cell cytoplasm, transforming the cancer damage condition toward a stage of normal. When the cell gets through an apoptosis process, it is produced K+ uptake inhibition. If Na+ remains outside of cell and K+ uptake is inhibited, the cell shrinks in an irreversible way. It produces the cell water to get out provoking a cell volume loss or cell shrinkage. Whether water and ions have been lost, shrinking cell and fragments would turn toward a permanent positive polarization of membrane-hCG associated molecule. This phenomenon may stimulate an attraction between apoptotic cell or its fragments and immune system cells. K+ and Na+ uptake inhibition by cell produces respectively electron inhibition efflux toward the extracellular space. Thus, cancer membrane positive charge, during or after apoptosis, remains unaltered. This well designed and intended mechanism by nature will produce the necessary attraction, between cancer and immune cells. Without ABA, those cells would remain immunologically inert. New investigations about ABA could suggest the real function of ABA as an endogenous cytokine when the hormone is released by human immune system cells. Bruzzone *et al*., (2007) [4] reported that, ABA has been identified as an endogenous cytokine in human granulocytes. They mention that, ABA stimulates several functional activities as phagocytosis, reactive oxygen species (ROS) and nitric oxide production, and chemotaxis of human granulocytes. In agreement to this research, increase of free intracellular ABA and its release by activated human granulocytes indicate that, ABA should be considered as a new pro-inflammatory cytokine in humans.Cancer cells are generally recognized and destroyed by immune system cells, but sometimes such cells evade the immune system. Actually, it has been discovered that immune cells as granulocytes use ABA for cell destruction. Herein, it is important to mention that, under a treatment with ABA, RARBETA is expressed and not silenced by cancer cell. The expression of this receptor has been confirmed by Zhao *et al*. 2007, in the Key Laboratory of Oral Biomedical Engineering of Ministry of Education, in Sichuan University. The research titled "Effect on Induction of Differentiation of TCA8113 Cells Affected by Abscisic Acid *in vitro*", confirms the expression of RARBETA, involucrin protein and caspase-3 mRNA.

1.11. ABA Against Human Stress

ABA is considered a hormone biologically designed by nature to defend plants against stress. ABA enhances plant adaptation to various stresses such as cold tolerance, salt osmotic adjustment and drought (Zeevaart *et al*., 1988) [26]. In addition, ABA-glucose ester (physiologically inactive form of ABA) accumulates in plant tissues with the age and during stress treatments (Dietz *et al*., 2000) [9]. Those considerations could open new insights and investigations concerning ABA.

1.12. ABA G-Protein Signalling Pathway

Coursol *et al*. (2003) [6] showed that a metabolite denominated, sphingosine-1-phosphate (SIP), functions in animals as an intracellular messenger and an extracellular ligand for G-proteins-coupled receptors of the receptor family, regulating diverse biological processes. In this research it was discovered in Arabidopsis that, SIP is a signalling molecule involved in ABA regulation of guard cell turgor. It also was reported that, an enzyme responsible for SIP production, sphingosine kinase (SPHK), is activated by ABA in Arabidopsis thaliana and is involved in both, inhibition of stomatal opening and promotion of stomatal closure. In human cells, ABA G-protein signalling pathway has been confirmed. ABA stimulates several functional activities in human granulocytes (Bruzzone *et al*. 2007) [4] and stimulates insulin release in human pancreatic islets (Bruzzone *et al*. 2008) [3]. Both researches point out that, ABA effect is produced through an identical signalling pathway sequentially involving a pertussis toxin (PTX)-sensitive G protein/receptor, protein kinase A activation, ADP-Ribosyl cyclase

phosphorylation, and consequent cyclic-ADP ribose over-production, leading to an increase of the intracellular Ca2+ concentration.

1.13. ABA application in pharmaceutical medicine

A pharmaceutical medicine for an intravenous, intramuscular and subcutaneous treatment may be elaborated by using the buffer system as mentioned before. ABA concentrations can range between 0.1 mg/ml and 5 mg/ml and best range would be between 1 mg/ml and 3 mg/ml. Medication will be prepared by obtaining an isotonic solution not higher than 9 mg/ml (0.9% W/V). Doses range between 0.1 mg/kg and 5 mg/kg. Liquid volume of the medications may vary between 5 ml (injections) and 25 ml (infuses). ABA in plants is conducted from roots to leaves via across the xylem, by which the ABA best application for a cancer treatment would be by intravenous way. ABA application via the human circulatory system would mimic ABA hormonal flow in plant streams and xylems. Destruction of cancer tissues by any treatment also it brings to a process of released toxins, which might poison other tissues conducting to coma and death. Therefore, it is recommended in a patient recovery process any method for detoxifying the human organism during ABA treatment. It is recommended an use of an ABA buffer medication for inducing cell normalization to: patients with a critical health condition; in terminal types of cancer; patient with inoperable large tumors; for elderly patients and for those in which toxins can compromise the patient life or vital organs; and for patients with damaged organs of excretion as colon, kidneys and liver. Likewise, it is recommended ABA buffer medication for inducing apoptosis to: cancer patient with moderate or relatively good condition; in early stage of cancer; young patients; and in those with small tumors where toxin unload released from cancer cell destruction or apoptosis does not compromise the life of a cancer patient. During the fabrication of the medication, the election of the ABA active ingredients is important. it has been pointed out, differences in ABA catabolism and uptake, between natural ABA and racemic compounds. According to Mertens *et al*. 1982, in leaf discs of V. Faba, natural ABA (S) was catabolized much more rapidly than the racemic ABA (R), the half-lives were 6-8 hours and 30-32 hours, respectively (cited in Zeevaart *et al*. 1988) [26]. It can be concluded that ABA as medicine to fight cancer and the disease, is evident and can be perceived through the invention. Any medicine proposed for cancer must come into the conjunction of the recovery process mechanism of Dr. Gerson. Apparently, the electron transfer in cancer cell membrane is just a consequence of a chain of reactions caused by ABA. Electron transfer is a complex and transient event in the middle of diverse and multiple reactions.

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