Biotechnology Reports 35 (2022) e00748

Contents lists available at ScienceDirect

Biotechnology Reports

journal homepage: www.elsevier.com/locate/btre

Review

The bioactive potential of phytohormones: A review

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ARTICLE INFO

Keywords:
Plant hormones
Microbes
Cell growth regulation
Disease
Human health

ABSTRACT

Plant hormones play an important role in growth, defence and plants productivity and there are several studies on their effects on plants. However, their role in humans and animals is limitedly studied. Recent studies suggest that plant hormone also works in mammalian systems, and have the potential to reduce human diseases such as cancer, diabetes, and also improve cell growth. Plant hormones such as indole-3-acetic acid (IAA) works as an antitumor, anti-cancer agent, gibberellins help in apoptosis, abscisic acid (ABA) as antidepressant compounds and regulation of glucose homeostasis whereas cytokinin works as an anti-ageing compound. The main aim of this review is to explore and correlate the relation of plant hormones and their important roles in animals, microbes and plants, and their interrelationships, emphasizing mainly human health. The most important and well-known plant hormones e.g., IAA, gibberellins, ABA, cytokinin and ethylene have been selected in this review to explore their effects on humans and animals.

1. Introduction

Hormones are generally defined as the class of signalling molecules that are released or secreted from specific glands in organisms and are transported by the circulatory system to the specified targeted organs to regulate physiology and behaviour [1]. The term hormones are sometimes extended to include some important chemicals compounds produced by specified cells that affect same or other cells [2]. In the specified targeted cells, hormones bind to a specific receptor, resulting in a change in the cell function and the activation of the signal transduction pathway inside the cells [3]. In the plant cell, there are no specific hormone-secretion glands, but there are some small signals molecules/compounds produced within the plants in extremely low concentrations called hormones. These regulate the specific cellular processes in the certain targeted plant cells, with the site of function varying from the production area to other organs where they have to function [4].

Our main emphasis on five primary plant hormones that were well studied include auxins, gibberellins, cytokinin's, abscisic acid and ethylene [5]. Some chemical analogues of plant hormones work differently in different systems, such as an auxin-like chemical compound, 2, 4-D or 2,4-dichlorophenoxyacetic acid, was developed to work as an herbicide in the USA (1945), which was the earliest plant growth regulatory pesticide product [6]. Other plant hormones like gibberellins, cytokinin's, and ethylene are also available in the market as a plant growth regulatory component. Plant hormones are known to work in plant growth and development. But recent study suggests that the plant hormones also work on human against different disease [7]. Synthesis of certain specific plant hormones, like, ABA, has been found not only in the plants system, but also in cyanobacteria, fungi, different animals and human beings [8]. ABA regulates animal's cell growth and differentiation, and improved the immune response in the presence of various stimuli [9]. Cytokining also help in the cell growth and development, anti-stress components [10, 11]. Auxin plays a crucial role as anti-tumour agent in human cell [12], where Gibberellin influences the antioxidant property [13]. In this review, we have attempted to explore plant hormones with the process of biosynthesis and chemical synthesis for their functional relevance in agriculture, microbial cells and the human body, and their potential applications in human health improvement.

2. Can plant hormones affect human physiology?

Plants and microbes have shaped the whole environment of the earth for millions of years [14]. Plant hormones regulate the plant physiology, shape and associated microbial environment [15]. But some microbes

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https://doi.org/10.1016/j.btre.2022.e00748
Received 31 January 2022; Received in revised form 31 March 2022; Accepted 7 June 2022
Available online 8 June 2022
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show commensalism, mutualism, symbiosis, and/or harmful microbes that release and mimic some essential plant hormones to alter plant hosts and their microbial communities [15]. A very poorly appreciated fact is that animals (mainly humans) produce and are affected by plant hormones [16]. Occasionally, these plant hormones affect glucose metabolism, inflammation, antioxidant response, cellular processes, cell division, cell cycle regulation, cancer etc. (Table 1, Fig. 1) [16]. The plant hormones have a great role in human and microbial cells that are accrued either by processed diet or directly through ingestion of raw plant material. We tried to explore this poorly investigated area and illustrate it with proper examples that how plants hormones directly or indirectly affect human and microbes' health.

3. Synthesis of phytohormones as bioactive compounds

3.1. Biosynthesis of phytohormones

The biosynthesis of auxin occurs via two major pathways, the first one is tryptophan dependant and the second is tryptophan independent. The flavin-containing monooxygenases tryptophan aminotransferases are known to synthesize IAA from L-tryptophan (Trp) via indole-3-pyruvate (IPA) [17]. Although, several other pathways have been identified for Trp-dependant IAA synthesis of auxin such as β-oxidation of indole-3-butyric acid (IBA) or by hydrolysing IAA conjugates, indole-3-acetamide (IAM), tryptamine (TRA), and indole-3-acetaldoxime (IAOX) pathways. Despite plants, some bacteria are also known to produce IAA by indole-3-pyruvate, indole-3-acetamide, and indole-3-acetonitrile pathways [18, 19].

The biochemical pathway for Gibberellins (GAs) synthesis involves 3 stages starting from GGPP (geranyl-geranyl diphosphate) via IPP (isopentenyl diphosphate) and is catalysed by many enzymes located in different parts of a plant cell. The first step occurs in the proplastids catalysed by enzymes which results in the formation of ent-kaurene. Oxidation of ent- kaurene formed GA12-aldehyde in the second stage is then catalysed by cytochrome P-450 monooxygenases in the endoplasmic reticulum. The third stage of the pathway is catalysed by 2-oxoglutarate-dependant di-oxygenases in the cell's cytosol to form GA [20]. In fungi, GA synthesis takes place by the MVA pathway which provides IPP for the synthesis of GAs [21]. Currently, there are 136 GAs known to be produced by fungi. Some plant growth-promoting rhizobacteria are also known to produce GAs [22].

Synthesis of ABA in plants involves 2C-methyl-D-erythritol-4-phosphate (MEP) pathways that occur in plastids by the production of carotenoids and a sequential conversion of zeaxanthin into xanthoxin and finally into active ABA [23]. Whereas in fungi, ABA synthesis takes place by the mevalonic acid (MVA) pathway via farnesyl diphosphate (FPP) intermediates [24].

The biochemical reaction of ethylene synthesis occurs through the methionine dependant pathway that starts with the conversion of L-methionine into S-adenosylmethionine (SAM) and this step is ATP dependant which is catalysed by the enzyme SAM synthase. This SAM is subsequently converted into 1-aminocyclopropane −1- carboxylic acid (ACC) by the enzyme ACC synthase (ACS). The final biochemical reaction of ethylene biosynthesis is the conversion of ACC into ethylene by the presence of an enzyme ACC oxidase (ACO) [25]. Some of the pathogenic bacteria produce ethylene through the utilization of arginine and α–ketoglutarate in the presence of an ethylene-forming enzyme (EFE) [26].

The biosynthesis of cytokinin occurs via isopentenyladenine-dependant and isopentenyladenine independent pathways. In isopentenyladenine-dependant pathway, the initial process of production of tZ cytokinin is the formation of isopentenyladenine (iP) nucleotide (iPRDP/iPRTP) catalysed by adenosine phosphate isopentenyl transferase (IPT). As substrates, IPT may utilize ATP, ADP, or AMP, and as prenyl donors, dimethylallyl pyrophosphate (DMAPP) or hydroxymethylbutenyl pyrophosphate (HMBPP). Further, iPRDP/iPRTP catalysed by CYP735A into tZ nucleotide and phosphoribohydrolase convert this inactive tZ into active tZ [27,28]. In isopentenyladenine independent pathway, tZ type cytokinin formed through shifting the hydroxylated side chain of HMBDP to the adenine ring [29,30].

Table 1
Plant hormones and its function.

Hormones	Organism	Functions	Reference
ABA	Plants	Plant Developmental processes. Abiotic stress responses. Regulation of root growth & water conductivity. Regulation of stomatal closure under drought Condition.	[71] [69] [70] [72]
	Humans	Glucose homoeostasis. Pro-inflammatory action in stress condition. Antidepressant property found in mice brain. Induced cell innate immunity.	[93] [78]
	Microbes (Endophytes)	Signalling molecules for communication amongst species. Promote interaction between plant & Arbuscular Mycorhizal fungi.	[94] [73]
Cytokinin	Plants	Cell division, cell elongation and other biological Processes. Chloroplast differentiation, leaf expansion, Senescence, apical dominance, nutrient mobilization. Morphogenesis ad meristem activity. Signal transduction in stress condition.	[84] [85]
	Humans	Gerontomodulatory and anti-ageing property. Oxidative product of DNA, affect gene expression, cell Cycle, stimulation of Ca flux anti-stress compound. Anti-oxidant property in DNA. Found in the urine of humans as a product of tryptophan metabolism in cancer patients.	[82] [83]
	Microbes (Endophytes)	NA	
Auxin	Plants	Promote cell differentiation, vascular tissue differentiation, root tip initiation Induce ethylene production, development of seedless Fruit. Disease resistance	[47] [93] [65]
	Humans	Auxin has anti-tumour property Regulate cell cycle	[56]
	Microbes	NA	
Gibberellin	Plants	Stimulates shoot growth, extension of internode, flowering Stem growth, induce seed germination, fruit setting Inhibition of formation of free radical which induce lipid peroxidation.	[61] [59]
	Humans	Causes liver and DNA damage, antioxidant defence system Antitumor property	[95] [13]
	Microbes	Endophytic fungus *Porostereum spadiceum* AGH786 *Penicillium citrinum* and *Aspergillus fumigatus* – promote plant growth	[63] [65]
Ethylene	Plants	Fruit ripening, break bud and seed dormancy, regulate leaf growth and abscission of leaves	[88]
	Humans	Ethylene oxide- genotoxic carcinogen Synthesized during oxidative stress	[90] [91]
	Microbes	*Mucor hiemalis* Defence plants from abiotic and biotic stress	[92]

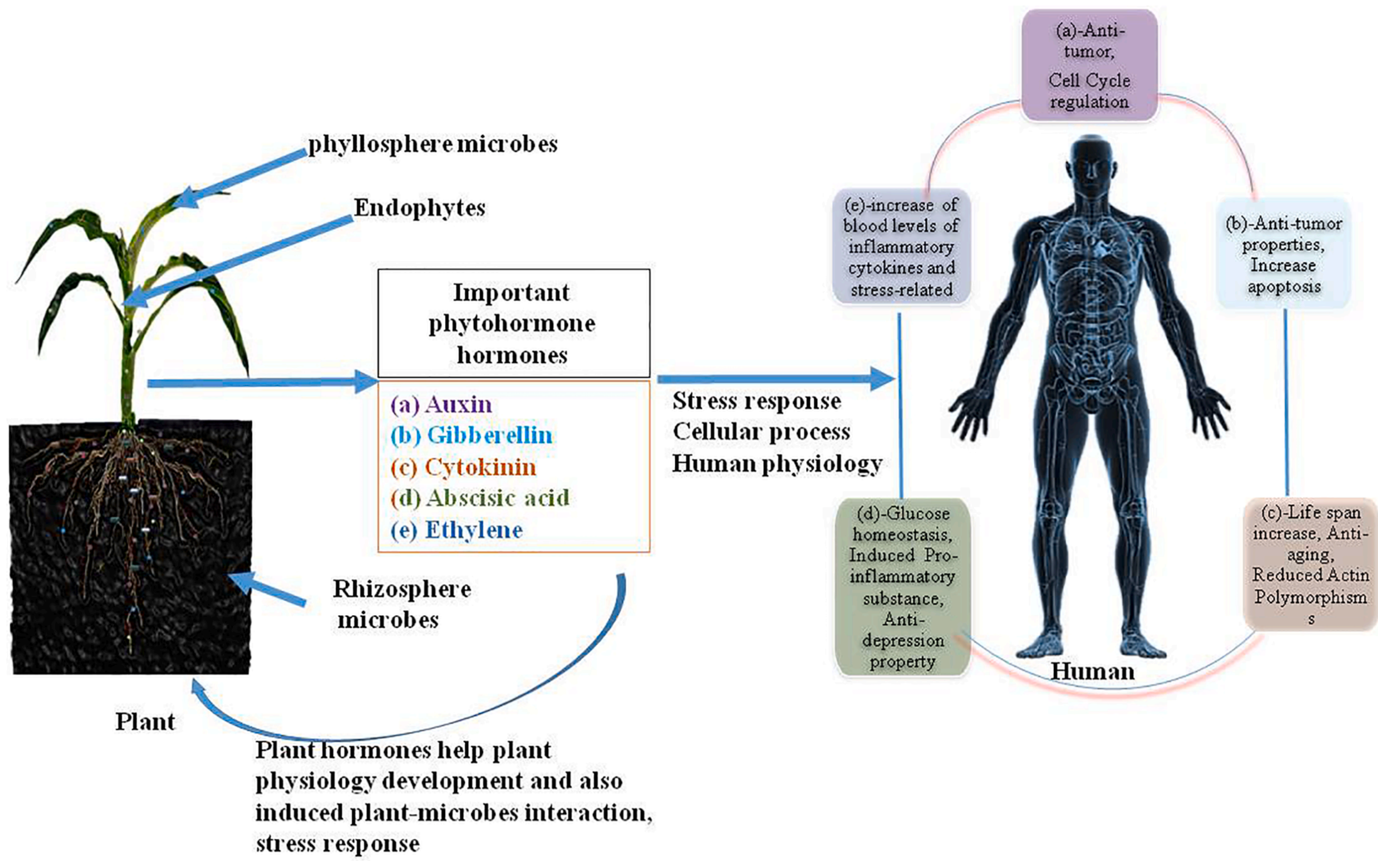

Fig. 1. Plant hormones function for plant and human health to interlink each other.

Cytokinin can also be synthesized in plants and bacteria through recycled tRNAs [31,32].

3.2. Chemical synthesis of phytohormones

Some synthetic compounds share chemical and structural analogies with naturally-occurring phytohormones. Boessneck for the first time evolved the mechanism for the synthesis of 1-naphthyl-acetic acid from naphthoyl chloride and 1-methylnaphthalene. Since then many mechanisms have been developed to obtain auxin-like compounds [33]. Savaldi-Goldstein [34] identified some synthetic analogues of 2, 4-dichlorophenoxyacetic acid (2,4-D), and 1-naphthaleneacetic acid (1-NAA) and termed them "Pro-auxins". These compounds can easily diffuse to the hypocotyl of the seedlings and undergo cleavage and hydrolysis for releasing auxins.

Kinetin was first synthesized in the laboratory by Miller and his coworkers in three different ways. First, it was isolated from herring sperm DNA by autoclaving it and five times extracted with ethyl ether. Second, direct alkylation of adenine with furfuryl chloride resulted in the formation of 6-furfurylaminopurine. Another experiment was performed by heating 6-methylmercaptopurine with furfuryl amine at high temperature and then at low temperature for many hours to obtain kinetin [35]. In the same way, Okumura et al. [36] synthesized BAP (6-benzylaminopurine) by condensing 6-methylmercaptopurine with 2–3 molecular equivalents of corresponding amines. In a study, the heterocyclic chemical derivatives of cytokinin such as 6-(3-hydroxybenzylamino) purine (meta-topolin) and 6-(2-hydroxybenzylamino) purine (ortho-topolin) along with their 9-glucosides and 9-ribosides were produced through the condensation of 6- chloropurine and its 9-glycosides with the addition of hydroxybenzylamine [37]. In another study, analogues of BAP were synthesized with various substituents attached to the phenyl ring [38] and adenine moiety was substituted at N1, C2, N3, N6, N7, C8 and N9 positions [39].

A group of synthetic analogues of ABA were synthesized and found more active than naturally occurring ABA that can be used as potential plant growth regulators viz., 2′,3′-benzoabscisic acid, pyrabactin, 2,3-cyclopanated and isoabscisic acid. 2′,3′-benzoabscisic acid was synthesized by treatment of 1-tetralones with MeI in the presence of NaH to introduce germinal methyl group to the adjacent carbonyl carbon to get (Z)−3-methylpent-2-en-4-yn-1-ol and n-butyllithium and other intermediates and finally these primary alcohols are oxidized into 2′,3′-benzoabscisic acid [40, 41].

Artificially synthesized chemical compounds structurally similar to ethylene are also produced. For example, ethephon (2-Chloroethylphosphonic acid) is a synthetic ethylene used to promote flower initiation, abscission, and fruit ripening. Ethephon is chemically synthesized through the acid hydrolysis of bis(2-chloroethyl)−2-chloroethylphosphonate mediated by hydrochloric acid (HCl). However, some of the other modified pathways for ethephon synthesis have been described by the Cauret [42]. Zhang & Wen [43] also reported the synthesis of ethylene gas by the decomposition of ethephon in a disodium hydrogen phosphate-buffered solution.

Yang et al. [44] synthesized 30 chemical derivatives of thiourea having gibberellin like activities. In general, these were derived through the substituted aniline (*for example,* 3-(trifluoromethyl) aniline) which was used to generate aromatic isothiocyanate compounds and then reacted with a substituted aromatic ethylamine to produce a thiourea derivative having two aromatic rings. However, some other chemical compounds are also synthesized such as AC94377 (1-(3-chlorophthalimido)-cyclohexanecarboxamide) [45] and 67D (1 ((*S*)−3-phenyl-2-(9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboximido) propanoic acid) [46] identified as GA, mimic and perform same function.

4. Plant hormones and their effects on human health

4.1. Auxin

Auxin is an important phytohormone, that performs a lot of functions in the plant including plant cell division, enlargement of a cell, stimulation of the vascular tissue differentiation, root initiation, tropic response and also delay in leaf senescence (Table 1, Fig. 1) [1]. Normally, IAA is produced from the apical meristematic region of plants shoots, buds and the tip of the root. The effect of auxins in plants is dependant on their concentration. The higher amount of auxin inhibits root elongation and vice versa [47]. It has been also reported that auxin synergistically interacts with ethylene, and leads to the development of the processes of root hair formation and root elongation, where the antagonistic activity shows hypocotyl elongation and lateral root formation in plants [48]. Gustafson in 1937 [49], for the first time, demonstrated that the application of auxins like components into the stigma of tomato and many other plants species causes the development of parthenocarpic fruit. During anthesis or probably after pollination and fertilization, the level of auxin and gibberellins consistently increased resulting in the development of seedless fruit. Auxin can induce biosynthesis of gibberellins and it can increase auxin levels in the ovary of plants [50]. It was reported that during plant defence, the auxin pathway behaves antagonistically with SA (Salicylic acid) pathway whereas the auxin and JA (Jasmonic acid) signalling pathway interact positively with each other [51]. Auxin and JA signalling pathways, share commonalities in providing resistance to necrotrophic pathogens. TIR1 and COI1 (F-box protein for Auxin and JA) get involved in providing resistance to several necrotrophic pathogens [52].

Auxin is also found in some parts of the mammalian body, mainly synthesized from an essential amino acid tryptophan which is consumed from different kinds of vegetables (soybean, broccoli, beans, onion and leafy vegetables) and other animals products, such as milk, cheese, red meat, chickpea, pumpkin seed, almonds and peanut (https://www.myfooddata.com/articles/high-tryptophan-foods.php). From a few previous studies, it was known that mammalian cells' function can be influenced by auxins. It was reported that auxin has a potential role to work as an antitumor agent [53]. Some recent scientific studies reported that in mammals, delay in cell cycle (S, G2 or M) progression in cells happened due to suppression of SCF typeubiquitin ligase function (by suppressing SKP2 dependant CDK2 and CDK4 activity) which induces G1 cell cycle arrest. For example, in ovarian cancer cells of humans, G1 arrest is caused by suppressing SKP2 which is the f-box protein of SCF complex and control proteolysis of CDK inhibitors including p27 and p21. Suppression of SKP2 reduced the progress of the G1 cell cycle and decreases the percentage of cells in S-phase with the help of auxin [53] (Table 1, Figs. 1 and 2).

Some microorganisms are reported that were able to produce auxin hormones. IAA producing different bacterial genera include *Pseudomonas, Azospirillum, Enterobacter, Streptomyces, Pantoea, Rhizobium, Azotobacter* and *Alcaligenes* [54–56] (Fig. 3). In various plants, microorganisms present in the rhizosphere can synthesize IAA as the secondary metabolite. For commercial IAA production, *Streptomyces griseoviridis* K61 and *Streptomyces lydicus* WYEC108 were used under trade name Mycostop [57]. Mainly IAA is produced by the microorganism helps plants directly or indirectly, consequently affecting humans (Fig. 1).

4.2. Gibberellins (GAs)

Gibberellins are also one of the most important phytohormones involved in plant growth promotion by degrading the negative growth regulator protein called DELLA [58] GA is known as a strong accelerator for shoot growth but shows very little response on root growth. To combat against different environmental stress conditions, various types of phytohormones are produced by plants that increase the potential to grow in such conditions. Gibberellin is one of the phytohormones secreted during stress conditions. The increased levels of GA3 were found in wheat and rice and enhanced growth under saline conditions [59]. GAs involved mainly in stem growth, induce seed germination by producing enzymes during seed germination and help in fruit setting and growth [1]. It was noticed that GAs inhibited the formation of free radicals which induce lipid peroxidation [58]. The most noticeable effect of GAs in plant growth was the extension of internode in shoot

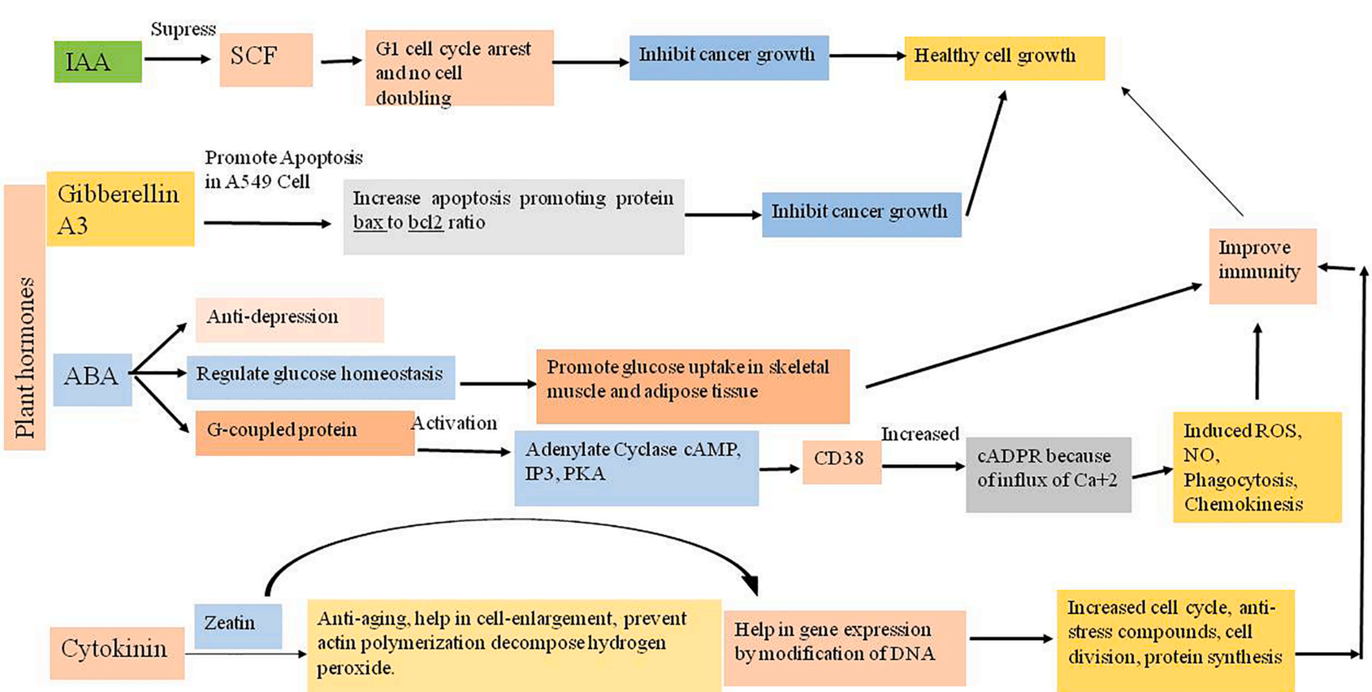

Fig. 2. Plant hormones and its application for modulation the biochemical and functional properties of human body.

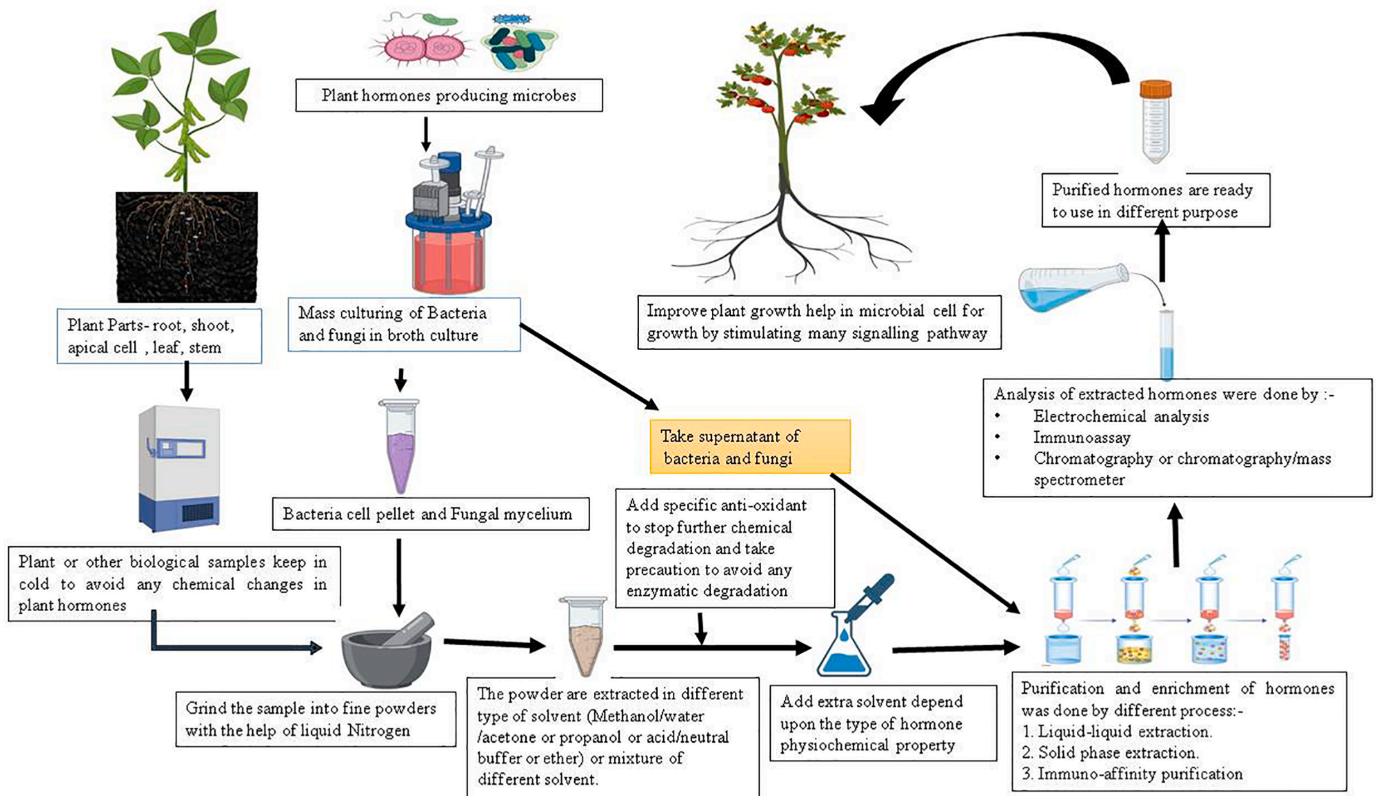

Fig. 3. Diagrammatic representation of plant hormones extraction and purification from plant and microbes.

growth and enhanced apical dominance and increased leaf growth. An increased amount of GAs has very little effect on a plant which shows increased dry weight. This indicated the secondary effect of GA on leaf growth. This secondary effect was mainly due to increase in carbon fixation [60]. Very limited studies have been done on the regulation of GAs in root growth. Externally applied GAs showed very little effect on the growth of roots in various plants. In several controlling developmental processes such as germination, growth and flowering, GAs interacts antagonistically with ABA [61].

Gibberellic acid in the human body comes from a plant diet (vegetables and fruits treated with gibberellic acid and some vegetables naturally produce gibberellic acids such as chilli and olive). The metabolic processes of humans can be influenced by the phytohormones present in our diet but the effect of GAs on humans is very less reported. GAs was reported as a potent pro-oxidant, that induce oxidative stress by generating reactive oxygen species (suppress the function of antioxidant enzymes activities) and causes hepatotoxicity in adult male albino rats by lipid peroxidation in the liver cells [62]. Cytogenetic effect of gibberellin A3 at different concentrations was noted in human lymphocyte culture. Gibberellin A3 induced chromosomal changes (by gap deletion, break), exchange between sister chromatids and DNA damage [63]. Zhang et al. [64] showed that a gibberellin derivative (GA13315) has an antitumor property against tumour cell lines in vivo as well as in vitro. GA13315 promoted apoptosis in A549 cells by increasing the level of apoptosis promoting protein (bax to bcl2 protein) ratio (Table 1, Figs. 1 and 2).

A mutualistic relationship is formed by rhizospheric bacteria with host plant, provides several benefits to them by siderophore production, increase availability of nutrient, nitrogen fixation, phosphate solubilisation and secretion of phytohormone. The different bacterial genera like *Pseudomonas, Bacillus, Azotobacter, Flavobacterium, Micrococcus, Rhizobium, Xanthomonas, Agrobacterium, Clostridium* and *Azospirillum* enhances plant growth and supresses phytopathogens [65] (Fig. 3). Endophytic microorganisms can produce phytohormones which help plants to alleviate various limiting factors such as salt stress and nutrition deficiency. It was found by Hamayun et al. [66] that an endophytic fungus *Porostereum spadiceum* AGH786 has the potential to produce GA which helps to alleviate salt stress and promote growth and health benefits in soyabean plant. Some of the endophytic fungi *Penicillium citrinum* and *Aspergillus fumigatus* have been reported to produce gibberellin in the rhizosphere and promote plant growth [67] (Fig. 3). Joo et al. [65] isolated a bacterial strain identified as *Burkholderia* sp. KCTC 11096BP through phylogenetic analysis 16S rDNA, produces GA and promote growth in cucumber and crown daisy. It has been reported that most pathogenic fungi and bacteria used GA as a secondary metabolite and this helps in plant-microbe interaction.

4.3. Abscisic acid (ABA)

Abscisic acid is an important phytohormone that takes part in various developmental processes such as seed and bud dormancy, regulation of opening and closing of stomata, controls size of various parts in plants, and works in environmental stress response. ABA shows an antagonistic relationship with GA in developmental processes such as seed dormancy and germination by promoting the biosynthesis of storage compounds and preventing precautious seed germination [68]. Under abiotic stress conditions, the expression of stress tolerance genes is regulated by phytohormone ABA, which enhances plant growth in an unfavourable environment [69]. It has been also reported that ABA induces root growth and control water conductivity under drought conditions [70]. ABA has a high heat tolerance capacity so that it can maintain its vitality under high temperatures and promotes seed development, vegetative growth and seed sprouting under ecological stress conditions [71]. In addition, ABA plays an important role in stomatal closure in plants under drought conditions when there was no need for CO_2 intake from the environment so that plants can reduce transpiration to prevent excess water loss from the plant body [72]. Biosynthesis of ABA in plants occurred in plastids through the MEP pathway by using carotenoid as a precursor molecule [73, 68]. It involves a series of enzymes mediating epoxidation of zeaxanthin, isomerization and cleavage of carotenoid into ABA molecules [74]. ABA also modulates plant defence responses through transcriptional reprogramming of plant cell metabolism and by inducing the expression of catalase which scavenge H_2O_2 [58]. Human beings and other animals are constantly exposed to ABA by various nutritional sources. Daily intake of fruits (i.e., apple, banana, apricot, avocado, fig, citrus) and vegetables (i.e., potato, tomato, soybean, barley, maize, pea, cucumber etc.) in our diet leads to the accumulation of ABA in our body [75]. High concentration of ABA in human body can be linked with a number of physiological and metabolic responses. Many studies have reported that glucose homoeostasis in a human being is regulated by ABA [76]. The adipose tissue of human releases ABA in low as well as in high glucose concentrations. In hyperglycaemia condition, release of GLP-1 induces β cells and insulinoma cells to release ABA and insulin which promotes glucose uptake in skeletal muscles and adipocytes. GLP1R is a glucagon receptor that stimulates GLP-1 to induce pancreatic β- cells for insulin secretion. It was also reported in rat myoblasts and murine adipocytes that ABA stimulates glucose uptake [77]. ABA is also known as an endogenous pro-inflammatory substance, released by animal cells during abiotic stress. Influx of Ca^{2+}inside the granulocyte is induced by ABA. The interaction between ABA and G-coupled proteins of plasma membrane trigger the activation of adenylate cyclase [AC], overproduction of cAMP, increase of IP_3, PKA mediated stimulation of CD38, and increased production of cADPR. This mechanism may be involved in influx of Ca^{2+} [71]. By this series of signalling pathway ABA also behaves as a pro-inflammatory endogenous cytokine as it stimulates phagocytosis, ROS and NO production, chemotaxis and chemokinesis and thus induces cell's innate immunity [78]. ABA also present in the hypothalamus and other parts of brain of mammals such as rodents and pigs. The amount of ABA in hypothalamus was found higher than any other tissues of mammals [79]. Endogenous secretion of ABA in the brain can be correlated with the stress response activity of hypothalamus. Antidepressant property of ABA was also reported in mice [79]. Thus, ABA rich food in our daily life could help to increase our innate immune responses and can also prevent different metabolic disorders like type 2 diabetes (Figs. 1 and 2).

4.4. Cytokinin

Cytokinin is a known phytohormone that occurs naturally as well as synthetically in the environment. Cytokinin is found naturally in plants and plays a vital role in cell division, differentiation and a number of biological processes such as apical dominance, leaf expansion and senescence, nutrient mobilization, chloroplast differentiation and activation of shoot meristem [80]. Deficiency of cytokine causes stunted shoot and smaller apical meristem. It is also found that cytokinin is important for morphogenesis and plant meristem activity in plants. In plants cytokinin plays an important role in signal transduction for different environmental stresses such as drought, salinity, and temperature via signalling pathways [81]. Cytokinin signalling pathway is regulated by His-Asp-phosphor lay; these components transmit the signal which triggers the CK responsive gene [81].

Other than plants, cytokinin is also found in different animals. At a very first, it was reported in an autoclaved herring sperm by Miller [82]. In mammals, cytokinin affects various physiological activities. Voller [83] discovered that cytokinin and their derivatives increased the lifespan in *Caenorhabditis elegans*. Zeatin, [6-[4-hydroxy-3-methyl-but-2-enylamino] adenine], a known cytokinin plant growth factor showed geronto-modulatory and anti-ageing properties in human skin fibroblasts in vitro. It has been experimented that long term treatment of zeatin in human fibroblasts can preserve cell vitality by reducing intracellular debris, cell enlargement, preventing actins polymerization and also by increasing the cell's ability to decompose hydrogen peroxide [84]. It has been reported that kinins are found in DNA as a product of oxidative, secondary modification and a secondary reaction of DNA, affecting different biological activities such as gene expression, inhibition of auxin action, stimulation of calcium flux, cell-cycle and as an anti-stress compound. It also induced cell division, cell differentiation and even protein synthesis in mammals [85]. Barciszewski, et al. [85] reported that high concentrations of kinins have been found in the urine of patients suffering from lung cancer. Cytokinins can be used as a marker for DNA damage as it protects DNA from oxidative stress, caused due to reactive oxygen species [ROS]. Kinetin is proven to have protective activities against oxidative stress in mammalian cells such as HL60 cells, HaCaT human keratinocyte cells, NRK rat epithelial kidney cells and human peripheral lymphocytes [86]. It has been found that cytokinin can protect cells from apoptosis and a low concentration of it can reduce stress mediated cell death [86]. Barciszewski et al. [87] hypothesized that endogenous Kinetin may arise as a consequence of oxidative damage of DNA, thus creating protection near the site of damage. Cytokinin bases have been shown to promote differentiation of keratinocytes. Kinetin at 40–200 lM concentration induces growth arrest and changes of several markers of differentiation (keratin K10 and involucrin) in human keratinocytes in cell culture [88] and also reported that treatment with Kinetin improved the sensitivity of ageing keratinocytes to the differentiating effects of Ca^{2+} ions (Figs. 1 and 2).

4.5. Ethylene

Ethylene is the only gaseous plant hormone that helps in, seed germination, flowering, sex determination, fruit ripening and abscission in plants. The regulation of growth and senescence of leaves is dependant on the concentration of ethylene. Ethylene interacts with other phytohormones either positively or negatively. In *Arabidopsis*, ethylene behaves antagonistically with abscisic acid on seed dormancy. Above a certain concentration, both inhibit elongation of the root. When the ethylene is treated with an ethylene synthesis inhibitor, its content gets lowered and ABA becomes effective in inhibition of root growth, this indicates that ethylene negatively interacts with ABA in root growth response [89]. Stepanova et al. [90] found that ethylene stimulates auxin biosynthesis for root growth promotion. They showed that tryptophan production is enhanced by stimulating WEI7 (Weak Ethylene Insensitive7) and WEI2 transcription which finally leads to auxin production in seedlings of Arabidopsis. Ethylene controls the level of auxin response factor [ARF] by regulating HOOKLESS1 [a member of N-Acetyltransferase gene family] in the hypocotyl region of plants which results in a well maintained and defined differential growth pattern found in these tissues [90]. It was found that ethylene concentration increased after interacting with herbivores. It could be due to oral secretory compounds which are secreted by herbivores and microorganisms that are transferred when insects feed on plant.

Ethylene comes from the natural metabolic process and through the air in the body of a human. In gut microflora of human, ethylene is present and can produce ethylene oxide, a known genotoxic carcinogen (IARC, Group 1) for human. In exhaled air of human, ethylene is also found [91]. Laurent et al. [92] reported that during systemic inflammation in humans, ethylene is produced. In systemic inflammation and infection, reactive oxygen species [ROS] induce oxidative stress which causes endogenous lipid peroxidation of unsaturated fatty acid and leads to ethylene formation (Figs. 1 and 2). Respiratory burst is responsible for oxidative stress and it occurs when bacterial and fungal infections encounter pathogen destroying blood cells (monocytes and neutrophils). ROS is produced in high amount due to this burst and causes oxidative stress. They showed that fatty acid (docosahexaenoic acid and oleic acid) significantly produces ethylene after exposing with Fe^{3+} ions which causes oxidative stress and leads to lipid peroxidation in cells. Microorganisms play an important role in maintaining plant health. In order to sustain in different environmental conditions, microorganisms induce the formation of different primary and secondary product which helps plant to alleviate different abiotic and biotic stress. ACC is known as a precursor of ethylene phytohormone. Plant growth promoting endophytes have ability to express ACC deaminase that protects plants from different abiotic and biotic stresses. It was showed by Primrose and Dilworth [93] that *Mucorhiemalis* produced ethylene in pure culture at a maximum rate under anaerobic condition.

5. Research challenges and future perspectives

The exogenous supply of these phytohormones in human body can affect the human gut microbiome and thus have an effect on metabolism and other biological activities. Many studies reported that gut microbes have the ability to produce these phytohormones but their concentration is not known. Endophytes found in fruits and vegetables having property to produce these hormones when consumed by human beings and can directly affect human health. It might show beneficial and harmful effects on human health. The genes responsible for the production of these hormones in microbes can be isolated and with the help of genetic engineering and their production can be regulated. This can be used in making drugs for treatment of various diseases, pharmaceuticals products and cosmetics. In the future research, omics data on the human whole microbiota study could be investigated to solve this unexplored mysterious question. Furthermore, the plant hormones play a key role in the signalling between plant and plant associated microbes, but its understanding between plant- animal–microbe interactions remains unexplored.

6. Concluding remark

The role of phytohormones is very well known in plants but very few studies have been done on the effect of these phytohormones in humans and other animals. Phytohormones have an effect on biological activities such as metabolic activity, disease resistance. For example, ABA and Ethylene have protective activity in metabolic diseases (Type-2 diabetes) and also induce cells' innate immunity. Hormones like Cytokinin and auxin directly quench reactive oxygen and induce anti-oxidant defences in human body. Cytokinin can be used as an active ingredient in cosmetics such as anti-ageing cream or beauty capsules and lotions. An effective concentration of cytokinin, GA and auxin can be used in treatment of cancer and tumour.

Author's declaration

All authors are aware about this communication. This is original review article and there is no conflict of interest between the authors and others.

Author's contribution

AM contributed to the preparation of the manuscript, its formatting and collection of data for writing and preparing figures. AKG, SS, SY and SB helped in creating figures and editing the manuscript. The main idea of this manuscript was designed by AM and JPV. Final editing done by JPV and SA

Declaration of Competing Interest

All authors are aware about this communication. This is original research manuscript. There is no conflict of interest between each author and others. There is no financial conflict of interest. Funding agency properly acknowledged in manuscript.

Acknowledgement

Authors thankful to DST (DST/SEED/SCSP/STI/2020/426/G; DST/INT/SL/P-31/2021), SERB (EEQ/2021/0001083) and Banaras Hindu University-IoE (6031) for financial support for research and development for enhancing sustainable agricultural productivity and microbiome study.

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