CHEMICAL REVIEWS

REVIEW

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Cross-Kingdom Actions of Phytohormones: A Functional Scaffold Exploration

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1. INTRODUCTION

Plant hormones, also referred to as phytohormones, are defined to be naturally occurring organic substances that influence at low concentrations plant physiological processes such as growth, differentiation, development, and response to abiotic and biotic stresses. As a matter of fact, "classical" plant hormones have been a research topic of numerous laboratories for centuries. Among them, plant growth regulators such as auxin, gibberellin (GA), cytokinin (CTK), abscisic acid (ABA), and ethylene, together with defense hormones including salicylic acid (SA), jasmonic acid (JA), and methyl jasmonate (MJ), have received long-time attention regarding the mechanism governing the key processes of plant development and physiology. As an array of functional biomolecules, some phytohormones were disclosed "unexpectedly" to possess substantial activities toward nonplant organisms in addition to the "traditional" function in living plants. These discoveries ended the "dormancy period" of the interesting area that used to be nearly neglected.

To one's surprise, JA, a plant stress hormone, exerted antitumor activity against human cancer cell lines.[1,2] Acetyl salicylic acid (Aspirin), a close relative of SA (a defense phytohormone), was demonstrated to be a potent inhibitor on mammalian cyclooxygenases.[3] This fundamentalizes at least in part why SA acetate registered as Aspirin early in 1899 remains the most widely prescribed anti-inflammatory and/or analgesic drug. These fascinating observations are compounded by indole-3-acetic acid (IAA, a predominant kind of auxin), which is remarkably active against some human cancer cells in the presence of horseradish peroxidase (HRP).[4] In the process of plant−microbe interaction, pathogens regulate the production and signaling responses of plant hormones to realize the successful infection, and the plant is obligated to produce phytohormones that act against the invasive bugs to rescue themselves.[5] This is exemplified by the involvement of phytohormone CTK in the interaction of a soilborne pathogen *Plasmodiophora brassicae* with some host plants belonging to the Brassicaceae family, where the fungus capable of producing CTKs independently is believed to downregulate the degradation of plant CTKs and induce the expression of CTK receptors.[6] Similarly, *Pseudomonas syringae* could use virulence factors such as AvrRpt2 (encoded by an avirulene (*avr*) gene *avrRpt2*) to elevate, during infection progression, the auxin levels to repress host plant defenses,

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thereby facilitating bacterial invasion and colonization.[7] Compounding the modulatory action of phytohormones on plant−microbe interaction, some phytohormones such as IAA or kinetin (also belonging to CTK) were found to be active toward plant-parasitic nematode *Globodera rostochiensis* by decreasing its surface lipophilicity, which is important in the nematode development during and after an adaptation to the host's tissue.[8,9] Moreover, strigolactones seem to have a wider spectrum of cross-kingdom actions than expected. (+)-Strigol, the first member of this group of lactones, was characterized early in 1972 as an effective germination stimulant of certain parasitic weeds such as *Striga* spp.[10,11] Later on, this compound was found to act as a signal molecule affecting the hyphal branching of some arbuscular mycorrhizal (AM) fungi.[12] Recently, strigolactones have been validated to regulate plant branching through the inhibition of the bud outgrowth, thus defined as a novel class of phytohormone.[13] Taken together, the versatile action of phytohormones on nematodes and microbes suggests the coevolved communication of plants with their neighboring organisms ranging from prokaryotes to lower eukaryotes. These well-ascertained findings on the topic raise new intriguing questions concerning the roles of plant hormones in mammalian and probably microbial cells and intensify the necessity to pay fresh attention to the cross-kingdom functions of these plant regulatory molecules.

Some experimentations suggested that plant and animal innate immunity system both involve perception of pathogen-associated molecular patterns (PAMPs) for protections against pathogens, and the comparable innate immunity systems are implicated in plant and animal defense responses.[14] This highlights at least qualitatively that some plant stress hormones such as JA and SA are distinguished molecules capable of acting on both plants and mammals. Therefore, it would be under expectation that JA and SA, maybe along with their derivatives, play crucial roles in basic cellular processes shared by or common to both plant and nonplant cells. Furthermore, the detailed recognition of such similarities or comparabilities between stress-associated hormone signalings of plant and animal cells would lighten the silent avenue to novel phytohormone analogues and compounds inspired by plant hormone with spectacular therapeutic efficacies, which may be used to conquer complicated human diseases such as cancers, cardiovascular disorder, and infections arising from drug-resistant pathogens.

The number of plant-derived therapeutical agents in preclinical trials is quite big, and the list of medically promising phytohormones is currently extending with the increasing interest and attention from the academy and industry, while the elucidation of the phytohormone signaling pathway in plants keeps progressing in a fascinating manner. Growing faster is the pile of evidence about how phytohormones and derivatives thereof are involved in nonplant cellular processes such as cell cycle, apoptosis, and membrane fluidity. These observations prompted us to review mainly from 353 references reporting the research progress and highlights of the topic under the following subtitles with an intention to illuminate suggestively the basic/common scaffold relating to the cross-kingdom actions of these molecules, and an emphasis will be put correlatively on the renewed knowledge valuable in the biomedical and agrochemical fields (Table 1).

2. JASMONIC ACID AND ITS ANALOGUES

Jasmonic acid (JA) and its methyl ester (methyl jasmonate, MJ) are fatty acid-derived cyclopentanones occurring throughout the plant kingdom to play important roles in both development and defenses against abiotic and biotic stresses like insect attacks and microbial infections. Chemically, jasmonates with diverse structures (Figure 1) collectively represent a family of oxylipin signaling molecules biosynthesized through the stepwise oxidation of polyunsaturated fatty acids. In response to a variety of stress factors including wounding, herbivory and pathogen infection, plant tissues display a rapid increase in jasmonate levels. However, in normal (or unchallenged) plant tissues, jasmonate is involved in carbon partitioning, mechanotransduction, senescence, and reproductive development.[15−18]

Interestingly, the "protective" functions of jasmonates in plants are so comparable to the health-maintaining effects of prostaglandins (PGs) that structurally resemble the former (Figure 1).[112] Concerning the generation, the liberation of linolenic acid from the plant membrane into cells initiates the biosynthesis of JA[113] in a manner analogous to the biosynthesis of PGs in mammalian cells, which involves the release from the membrane of arachidonic acid followed by the coversion into eicosanoids.[114] As to the function, jasmonates and PGs are remarkably similar in regulating the relevant biological processes including male fertility, ovary development, and antistress responses.[115] Regarding the distribution, jasmonates are ubiquitous in the plant kingdom while PGs and analogues thereof are widely present in mammals. However, this division of the hormone distribution is actually getting vague or at least not strictly distinct. For example, jasmonates have been detected as well in some lower eukaryotes such as fungus *Lasiodiplodia theobromae*,[116] and their ability has been supposed to regulate cellular processes in insects, supporting thereby the hypothesis that jasmonates are of general biological significance.[117]

The metabolism and function of resultant metabolites of jasmonates and PGs are also comparable (Figure 1). JA can be transformed via multiple pathways including methylation (to form MJ), conjugation (with amino acids to generate JA−amino acid conjugates), hydroxylation (to afford tuberonic acid-related derivatives), reduction (to yield cucurbic acid-related derivatives), and degradation (to supply jasmone). In contrast, PGs are de novo synthesized from membrane-released arachidonic acid when cells are activated by mechanical trauma or specific cytokines, growth factors, etc.[112] After generation from arachidonic acid, prostaglandin H_2 (PGH_2) can be converted into structurally similar PGs (such as PGE_2, PGD_2, $PGF_{2\alpha}$, and PGI_2) by different prostaglandin synthases. It is noteworthy that PGs probably activate an array of nuclear hormone receptors including peroxisome-proliferator-activated receptor-γ (PPAR-γ),[112] whose activation induces differentiation to cause apoptosis of some cancer cells.[118,119] This observation helps one to understand some of the antiproliferative mechanisms of jasmonates as detailed below.

2.1. ATP Depletion of Jasmonates

Both apoptotic and necrotic cell death are recognized to be closely related to mitochondrial perturbation. The antitumor action of jasmonates was recently disclosed in vivo and in vitro to target directly and selectively toward the mitochondria of intact human leukemia and hepatoma cell lines by evaluating the magnitude of mitochondrial swelling, and by quantifying cytochrome c release from mitochondria to cytosol. Furthermore, the selectivity of MJ against cancer cells was evidenced from the observation that it did not affect normal human 3T3 fibroblast cells and peripheral blood lymphocytes.[117,120] This finding could

Table 1. Updated Summary of Phytohormone Actions

phytohormones	plant cells	nonplant cells: animals	nonplant cells: microbes	remarks
JA and analogues	regulating plant growth (i.e., carbon partitioning, mechanotransduction, senescence), reproduction, development and immunity (defense responses to stresses)[15−18]	inducing apoptosis in tumor cells[1,19,117,120,125] and leukemia cell redifferentiation[2] perturbing mitochondrial ATP generation in cancerous cells[20]	participating in arbuscular mycorrhizal interactions;[24] inducing some fungi to synthesize terpene[25] and alkaloid;[26] serving as chemoattractant for some phythopathogenic bacteria[27]	co-involvement in defense responses of plant and animal cells; elevated mitochondrial ROS, and activated MAPK pathway; cyclopentenone/cyclopentane as the most probable functional scaffolds
SA and congeners	regulating plant growth and development, photosynthesis, stomatal closure/opening, and ion uptake; mediating plant SAR (changes in ion flux and ROS, activations of defense-related genes)[28]	antitumor;[29−37] neuroprotection[38,39]	antimicrobial[40−43] mediating fungal development;[44,45] involvement in plant−microbe interactions[46] increased antibiotic resistance of some bacteria[47,48] affecting PHA (polyhydroxyalkanoic acid) accumulation in *Pseudomonas aeruginosa*[49]	SA-dependent hypersensitive response in plants "resembles" the SA-mediated mammalian apoptosis in intracellular calcium increment, ROS generation, nitric oxide production, and MAPKs activation SA and some of its bioisosteres like anthranilic acid could be the functional scaffolds
auxins (predominantly IAA)	modulation of plant cell division, elongation, and programmed cell death[50,51]	antitumor action of IAA upon combination with HRP;[4,52,53] action of 5-hydroxytryptamine (an IAA analogue) as a mammalian neurotransmitter that attenuates plant leaf senescence[54,55]	antimicrobial action of some IAA derivatives;[56] modulating some plant−bacterium interactions[57]	"root-brain hypothesis" postulated by Darwin seems helpful in understanding the "inherent correlation" between the actions of IAA in plant roots and of 5-HT in mammalian brains;[58] indole moiety could be the most possible pharmacophore
CTKs	modulating plant cell division, elongation, and differentiation;[59,60] regulating sink formation (vacuolar invertases, cell cycle activity), leaf senescence, nutrient assimilation and uptake; involvement in the responses to some biotic and abiotic stresses[62]	antitumor activity with i^6A shown to suppress cancer cell proliferation, and to disturb DNA/RNA syntheses[61]	modulating rhizobium-legume symbiosis;[63−67] contributing to the virulence of some phytopathogens[68−73]	leading to cell cycle arrest and programmed cell death (apoptosis) in both plant and animal cells; inducing redifferentiation of plant callus similar to that of animal cancer cells;[74] *IPT* gene (encoding an evolutionarily conserved eukaryotic protein involved in the syntheses of plant CTKs) seems "comparable" to human *tRNA-IPT-1*, which is important in controlling tumor progression; adenine-like (isosteric) motif as the most probable functional scaffolds
GAs	regulating plant seed development, organ elongation, florescence, and fruit growth[75,76]	antitumor activity of GA analogues;[77] antidiabetic activity of GA and derivatives[78]	initiating the symbiosis of *Piriformospora indica* (a Basidiomycete) with its host roots[79]	tetracyclic diterpenoid skeleton shared by GAs could be the functional scaffold

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Table 1. Continued

phytohormones	plant cells	nonplant cells: animals	nonplant cells: microbes	remarks
BRs	affecting plant seed germination, rhizogenesis, flowering, senescence, abscission and maturation;	antitumor;[82−84]	antiviral[85,86]	analogous early events in signaling pathways of plant BR and mammalian TGF-β (transforming growth factor-beta) have been discerned;
	modulating vascular differentiation and signal transduction for pollen tube formation;	immunomodulatory[87,88]		particularly, the dimerization of BRI1/BAK1 and phosphorylation of BAK1 by BRI1 in the plant BR signaling seems well comparable to the heterotetramerization of RI and RII (a pair of receptor kinases) and RI phosphorylation by RII in the mammalian TGF-β signaling[89]
	improving plant tolerance to some abiotic stresses[80,81]			steroidal nuclei with appropriate oxidation patterns might be essential for the discerned activity
strigolactones	shoot branching regulators;[90−92]		hyphal branching stimulator of some AM fungi;[12,93]	similarity in modulatory mechanisms for fungal cell mitosis and bacterial cell division;
	parasitic weed germination stimulants[10,11]		stimulation of cell division of endocellular bacteria within certain AM fungi[94,95]	recognition of functional scaffolds awaits more investigations
ABA	regulating seed development and dormancy, as well as plant adaptive responses to abiotic stresses[96,97]	ABA signaling operation in lower *Metazoa* including marine sponges (in response to heat stress), and Hydroids (promoting regeneration);[98−100]	promoting the growth and development of some fungi;[54]	ABA-modulated signaling pathways in plants and animals all involve cADPR (controlling intracellular calcium), but LANCL2 was only found as a putative component of ABA-sensing protein complex in mammals;[107]
		antiinflammatory;[101]	modulating some arbuscular mycorrhiza (AM) development[106]	more work is desired for identifying functional scaffolds
		antiatherosclerotic;[102]		
		antidiabetic;[103,104]		
		modulation of calcium signaling in mammals[105]		
ethylene	regulating plant fruit ripening, and regulating responses to abiotic and biotic stresses jointly with JA[108,109]		modulating plant−microbe interaction[110,111]	modulating the crosstalk between SA and JA signaling;
				ethylene is chemically the common quasi-isostere of N_2, NO, and O_2, where the size of hydrogen (the smallest atom) is trivial

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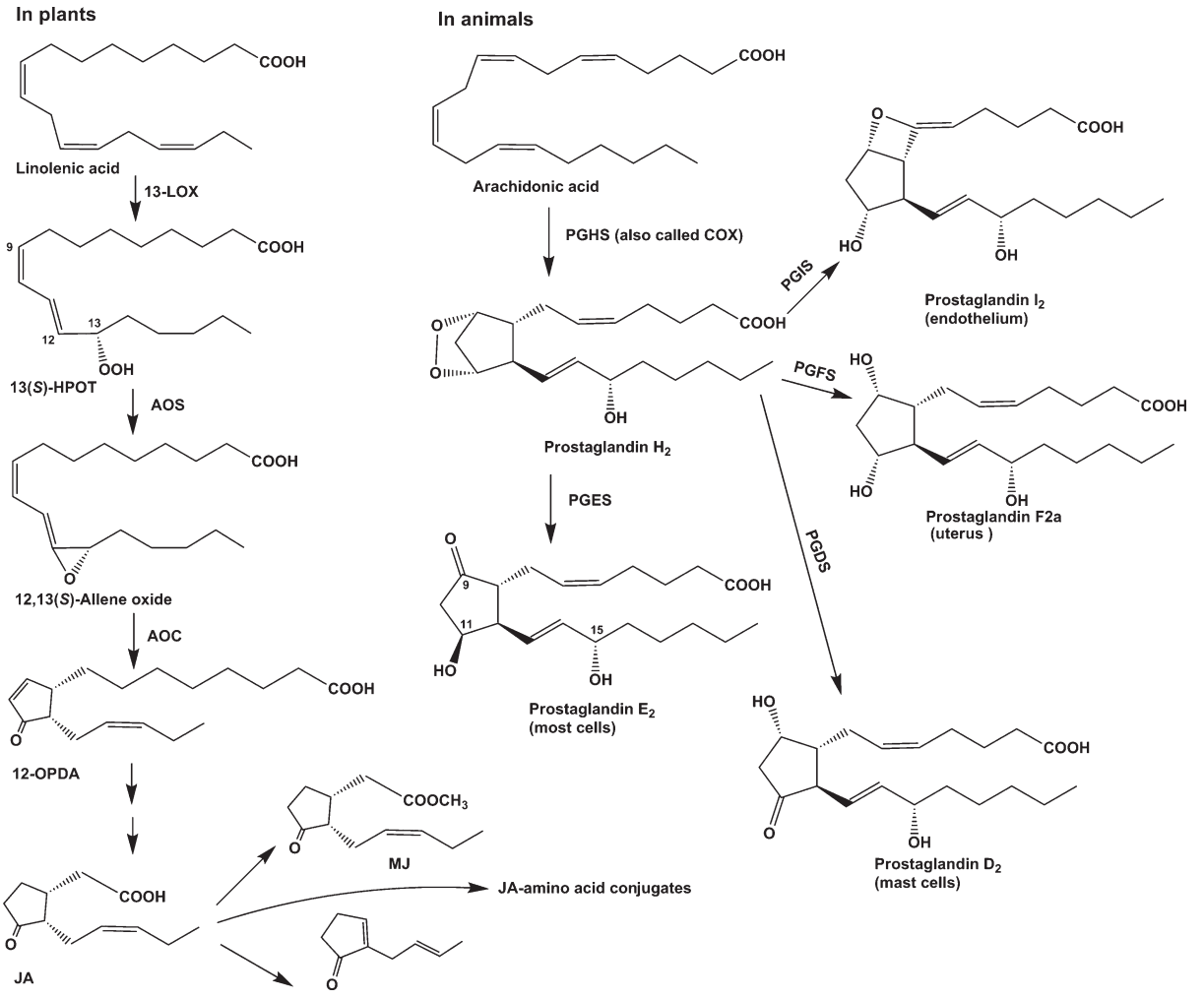

Figure 1. Biosynthetic and metabolic comparisons between jasmonates in plants and prostaglandins in animals.

be explained by earlier work reporting that the mitochondria of normal and cancer tissues differ in a few aspects.[121] The proliferation of cancer cells needs to modulate the expression of permeability transition pore complex (PTPC) components,[122] and to maintain higher mitochondrial membrane potential and increased rate of ATP generation through glycolysis rather than oxidative phosphorylation in the presence of oxygen (defined as the Warburg effect).[123,124] Moreover, MJ was proven to induce a rapid ATP depletion in B lymphoma cells.[125] Furthermore, MJ was shown to bind most likely to mammalian hexokinase to perturb its interaction with one of the PTPC components, the so-called voltage-dependent anion channel (VDAC), leading eventually to the dissociation of hexokinase from mitochondria and the release of cytochrome c.[20] As an initial and critical enzyme in the glycolysis pathway, hexokinase binds to the mitochondrial VDAC via a hydrophobic interaction.[126] This rationalized that the detachment of hexokinase from VDAC initiates mitochondrial perturbation to accelerate cell death.[21−23] Taken together, these data suggested that some jasmonates could act as a class of introductory molecules that force the cancer cells into "death tunnel" by depriving them of energy.

2.2. Induction of Leukemia Cell Redifferentiation

As suggested, the induction of redifferentiation may be employed as a strategy to "normalize" or "domesticate" undifferentiated cancer cells by modifying their genetic profiling, thereby causing a slower proliferation rate of cancer cells or even loss of their original neoplastic characteristics. Some retinoids have been demonstrated to function desirably in this way with all-*trans*-retinoic acid [capable of inducing differentiation of acute promyelocytic leukemia (APL) cells[128]] being approved for the clinical treatment of APL patients.[127] Presumably owing to the comparability of jasmonate with retinoids in polarity and structure, investigations were performed to explore the induction of jasmonate on cancer cell redifferentiation, showing that the human myeloid leukemia cell line HL-60 was substantially susceptible to MJ exposure. Furthermore, all-*trans*-retinoic acid and 1α,25-dihydroxyvitamin D3, two types of granulocytic and monocytic differentiation inducers, were shown to act synergically with MJ in the induction of the HL-60 cell differentiation, and the mitogen-activated protein kinase (MAPK) signaling pathway was concluded to play a key role in MJ-induced redifferentiation of HL-60 cells.[2] In the nitroblue tetrazolium (NBT) reduction assay, the recognized MAPK inhibitor PD98059 (2′-amino-3′-methoxyflavone) was disclosed to suppress MJ-induced differentiation in leukemia cells. Moreover, MJ also induces upregulation of the calcium-binding protein S100P in association with its inhibition on cancer cell growth.[130] In addition, S100P was shown to be essential to the cytokinin-induced redifferentiation in HL-60 cells based on mRNA upregulation of

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S100P during this process.[130] This observation deepened the understanding of the inducing action on the leukemia cell redifferentiation discerned previously with the cytokinin family of phytohormones.[129] Accordingly, some jasmonates and cytokinins may share in part the mechanism in redifferentiating human leukemia cells.[120]

2.3. Induction of Apoptosis

Basically the apoptosis of cancer cells is initiated by instrinsic and extrinsic pathways, and the former is mediated by mitochondria while the latter is done by death receptors on the cell surface.[131] The extrinsic apoptotic pathway involves a class of death receptor ligands including tumor necrosis factor-α (TNF-α), TNF-related apoptosis inducing ligand, and factor associated suicide (Fas).[132] Activation of these receptors recruits Fas- and TNF receptor-related death domains, which activate caspase-8 and MAPK to lead eventually to cell death.[133] As part of the extrinsic apoptotic mechanism, the MAPK pathway is essential to regulating a variety of downstream proteins such as kinases. Activation of MAPK results in signaling transduction to intrinsic apoptotic proteins, which culminates upon cell death. Initiation of the intrinsic apoptotic pathway decreases the mitochondrial membrane potential accompanied by releases of cytochrome c and other apoptogenic proteins from the mitochondria, forming the apoptosome (called alternatively the caspase-3 activation complex) and leading finally to cell death.[121,122] In fact, many chemotherapeutic drugs exert their antitumor actions by inducing cellular stress that may also afford mitochondrial perturbation and, ultimately, cell death.

In the light of apoptotic pathways, some jasmonates such as *cis*-jasmone (CJ) and MJ were disclosed to act toward breast cancer cell lines MDA-MB-435 and MCF-7 by suppressing the long-term cancerous cell proliferation as evidenced from the cell arrest at G_0/G_1 and S phases with increasing apoptotic cell population after CJ and MJ administration. Further studies showed that MJ could reduce the membrane fluidity to activate both extrinsic and intrinsic apoptotic pathways in the treated cells. As an indication of the activated extrinsic apoptotic pathway, an elevated expression of TNF receptor 1 was discerned, followed by activations of MAPK and caspase-8. Moreover, MJ resulted in the reduction in the mitochondrial membrane potential and activation of caspase-3 in breast cancer cells, indicative of the activation of the intrinsic apoptotic pathway.[19]

It is noteworthy that reactive oxygen species (ROS) including superoxide ion, hydrogen peroxide, hydroxyl radical, and singlet oxygen may be involved in MJ-induced apoptosis. This was confirmed by the recognition that MJ-induced apoptosis could be inhibited by antioxidants such as *N*-acetyl cysteine and catalase in A549 human lung adenocarinoma cells.[134] The same group reported that the MJ treatment increased the level of Bax and Bcl-Xs, two proapoptotic members of the Bcl-2 family, without affecting the level of antiapoptotic proteins Bcl-2 and Bcl-X_L.[134] These suggested that the MJ-induced apoptosis of A549 cell might also be mediated through a cascade associated with the release of hydrogen peroxide, and the elevated expression of pro-apoptotic proteins. This was reinforced by the subsequent observation that, upon MJ exposure, MJ could induce heat shock protein 72 (HSP 72) in C6 glioma cells with the coincrement in cellular hydrogen peroxide, superoxide ions, and mitochondrial ROS.[135] More recent experimentation with MJ and JA demonstrated a strong correlation between the mitochondrial superoxide (MSO) formation and the reduced cellularity in the acute myelogenous leukemia (AML) cell line.[136]

2.4. AKR1C Enzyme As a Cellular Target for Jasmonates

Using AML cell lines HL-60 and KG1a, JA and MJ were shown to act toward aldo-keto reductase 1C (AKR1C), an important member of the AKR superfamily covering NAD(P)(H)-dependent oxidoreductases that are involved in some physiological processes.[136] Previously, AKR1C3 was demonstrated to be most likely a novel regulator of myeloid cell differentiation, suggesting that it could serve as a potential therapeutic target for leukemia treatment.[34,137] This was subsequently substantiated by the rapidly emerging evidence demonstrating (1) that the differentiation of neutrophils and monocytes can be promoted by the treatment of AML cells HL-60 with the AKR inhibitors indomethacin and medroxyprogesterone acetate; (2) that an overexpression of AKR1C3 inhibits HL-60 differentiation; and (3) that knockdown of AKR1C3 in human leukemia K562 cells leads to erythroid differentiation.[34,118,137,138] Furthermore, the AKR1C3 enzyme was proposed to be a profitable cellular target for treating prostate and breast cancers.[139−141] Other independent groups have recommended AKR1C1 and AKR1C2 enzymes as potential targets in some solid tumors including prostate, breast, lung, and bladder cancers.[141−144] Similarly important is the observation that AKR1C enzymes activate xenobiotic polyaromatic hydrocarbon (PAH) carcinogens in vitro since the PAH-rich fossil fuel combustion emission is one of the high-risk factors for lung cancers. In particular, the polymorphism of AKR1C3 is actively involved in modulating the risk for many tumors such as lung cancer, diffuse large B-cell lymphoma, and prostate and bladder carcinomas.[145−149] The AKR1C3 enzyme can catalyze the conversion of PGD_2 into 9α,11β-$PGF_{2\alpha}$ (9α,11β-$PGF_{2\alpha}$).[150] Alternatively, PGD_2 dehydrates spontaneously to yield J-series PGs culminating in the formation of 15-deoxy-$\Delta^{12,14}$ PGJ_2 ($15dPGJ_2$), which is highly active in the inhibition of nuclear factor-κB (NF-κB) together with the ROS elevation.[136,151] Along with the structural similarity between jasmonates and PGD_2 (Figure 1), the renewed understanding on the AKR1C3 enzyme supported the hypothesis that AKR1C3 could represent one of the important antitumor targets, toward which jasmonates may act like some PG analogues.

2.5. Cyclopentenone and Cyclopentane As Antitumor Scaffolds

Scrutiny of chemical structures of jasmonates and PGs as well as other cytotoxic compounds such as clavulones suggested that the cyclopentenone moiety could be an antitumor pharmacophore, which may act toward intracellular targets in the cancer cell mitochondria. A review summarized other types of cyclopentenone-bearing compounds with antitumor activity, highlighting that the cyclopentenone scaffold is of value in designing new anticancer drugs.[152]

Concerning the reason why the cyclopentenone moiety can interact with a variety of cellular targets including nuclear factors and some components on cancer cell mitochondria, the α,β-unsaturated carbonyl group of cyclopentenone is an electrophilic center susceptible to addition reactions with nucleophiles such as free sulfhydryl groups of reduced glutathione (GSH) or cysteine residues in proteins (Figure 2). Alkylation of key cysteine residues may lead to inactivation or defunctionization of the targeted proteins.[153]

The inclusion of the cyclopentenone moiety increases remarkably the anticancer potency of several anticancer molecules such

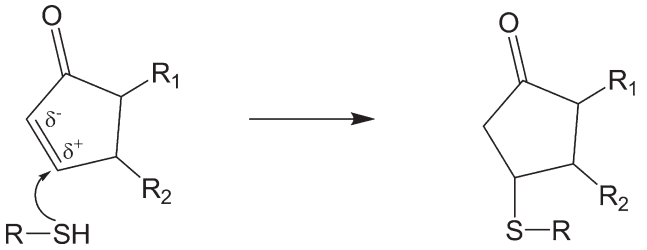

Figure 2. Interaction of cyclopentenone with some nucleophile motifs as represented by exposed cysteine residues in proteins.

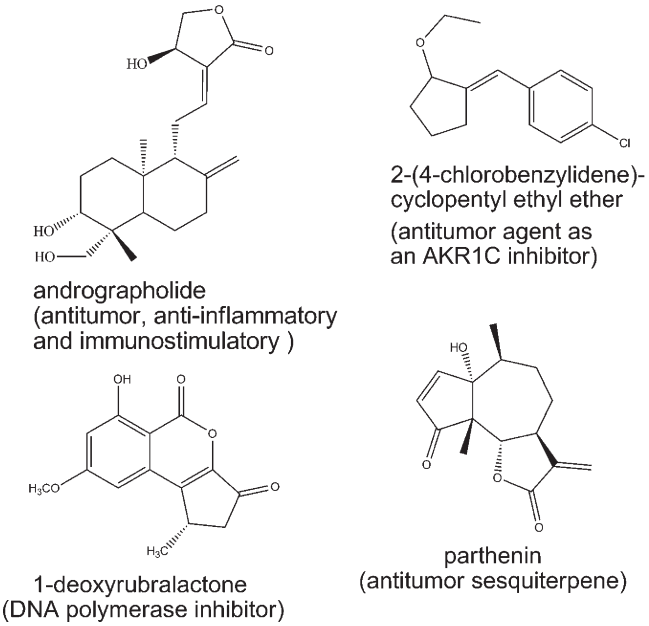

Figure 3. Other bioactive compounds containing cyclopentanyl or cyclopentenonyl scaffolds.

as jasmonates and chalcones.[154] This is distinctly exemplified by MJ, a newly identified anticancer agent targeting cancer cell mitochondria.[120] Furthermore, the introduction of the cyclopentenone residue into MJ greatly boosts its differentiation-inducing and growth-inhibiting activity in myelomonocytic leukemia HL-60 cells.[2]

Interestingly, AKR1C1 and AKR1C3, proven to be promising targets for cancer prevention and therapy, are susceptible to some isosteres of cyclopentenone as substantiated by Štefane and co-workers.[155] Such compounds as 2-(4-chlorobenzylidene)-cyclopentyl ethyl ether (with correct construction of a cyclopentane scaffold, Figure 3) were tested to substantially inhibit AKR1C1 and AKR1C3 enzymes. This finding may be important to the understanding of mode of action of other cyclopentenone- or cyclopentane-containing bioative derivatives like andrographolide,[156] 1-deoxyrubralactone,[157] and parthenin.[158]

As a whole, cyclopentenone and most possibly cyclopentane moieties may represent the functional scaffolds for the antitumor activities of jasmonates because of their interaction with a variety of cellular targets like AKR1C enzyme isoforms in mammalian cancer cells. The finding would provide the promise of some cyclopentenone- and/or cyclopentane-bearing compounds as adjunctive therapeutics for treating cancer and other diseases where those targets are involved. To sum up, the jasmonate—cancer interaction may involve two seemingly contrary aspects: induction of apoptosis versus redifferentiation of cancer cells. The linkage between the redifferentiation of cancer cells and the suppression of tumor proliferation suggests that the redifferentiation mechanism may be central to the antitumor activity of jasmonates. The other two cell death-associated mechanisms (the ATP depletion and apoptosis induction) appear to be involved in the antitumor function due to the emerging evidence that suppressors of the mitochondrial perturbation and of ROS have negative effects on the antitumor activity of jasmonates.[134] Furthermore, jasmonates have been reported to kill drug-resistant cancer cells.[159] Generally, the drug resistance is thought to be conferred by either p53 mutation or P-glycoprotein (P-gp)-mediated efflux pump. Jasmonates have been demonstrated to bypass drug resistance in mutant p53-expressing B lymphoma cells by inducing a nonapoptotic cell death.[123] Using two clones of melanoma cells, one with low-level P-gp expression and the other with P-gp overexpression, jasmonates were shown to circumvent drug resistance endowed by an overexpression of P-gp.[159]

Investigations with jasmonates in mammalian cancerous cell lines have unraveled a surprising but not totally unexpected rationale that this type of plant hormone is also able to induce defense responses in animal cells, referred to as heat shock response.[135] Distinct evidence came from the elaborate work by Ishii et al.[2] and Oh et al.[135] The former group has demonstrated that HL-60 AML cell differentiation initiated by MJ is correlated with MAPK activation, and the latter has reported that MJ might induce HSP 72 in C6 glioma cells without affecting cell viability, but with the epiphenomena that intracellular and mitochondrial ROS were increased in response to MJ. Given that the MAPK activation is a downstream event of jasmonate signaling pathway in plants,[160] and that the increased mitochondrial superoxide (MSO) is associated with the MAPK activation during myeloid differentiation,[161] an inherent linkage exists most likely between MJ-induced mitochondrial ROS and the MAPK activation in mammalian cells. In other words, the actions of JA toward some mammalian cells may share certain common signaling events such as defense responses triggered by this phytohormone in plants.

3. SALICYLIC ACID AND ITS CONGENERS

The antitumor activity of aspirin (2-acetoxybenzoic acid) was initially recognized from the finding that tumor metastases were remarkably reduced in rats with thrombocytapenia. Additionally, the PG level is elevated in rat colorectal tumor tissue, suggesting that the beneficial effects of aspirin against cancer could be mediated through inhibition of cyclooxygenase (COX). A variety of epidemiological studies and experimentations in animals reinforced the presumed inverse relationship between the cancer incidence and the administration of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).[3]

The hypersensitive response of plants upon pathogenic attacks is similar in principle to mammalian apoptosis because both processes include a lasting elevation in cytoplasmic calcium, ROS generation, nitric oxide production, and MAPKs activation, leading to cytoplasmic shrinkage, chromatin condensation, and DNA breakdown.[162,163] If bereaved of essential nutrients and limited within a local region, the pathogen suffers from rapid cellular changes to result in cell death. During the hypersensitive

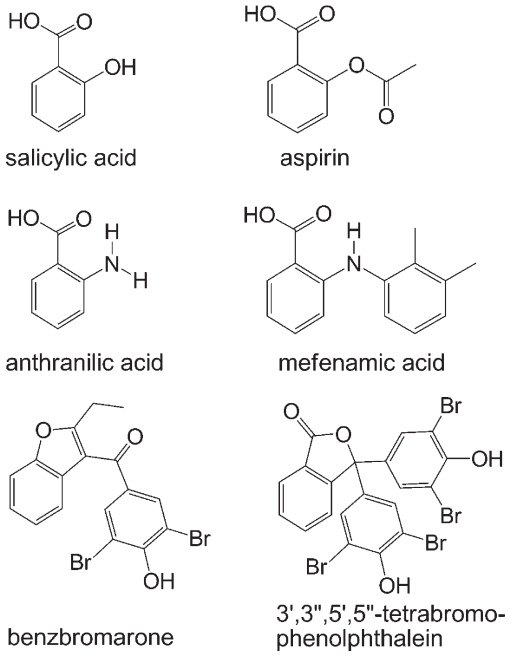

Figure 4. Structure of phytohormone salicylic acid and its bioisostere anthranilic acid as well as the related molecules possessing SA-based scaffolds.

response, salicylic acid (SA, Figure 4) potentiates the oxidative burst arising from the generation of ROS including hydrogen peroxide and superoxide, which speeds up the cell death.[164−166] Therefore, the SA-mediated hypersensitive response in plants can be thought to be a form of programmed cell death (PCD), killing invading pathogens and/or limiting their spread.[167]

The similarities between plants and animals in the context of stress responses mediated by SA signaling molecule may suggest the presence of common cellular components and/or pathways across the eukaryotic organisms. As reviewed by Pierpoint,[168] the medicinal properties of salicylates in human are a logical result of their roles in plants. The endeavor to elucidate the fundamental biological processes in response to external stimuli, such as pathogens, viruses, and carcinogens, would pave the avenue for conquering the human cancer and other high-risk diseases as discussed below.

3.1. Antitumor Activity

Epidemiological studies have suggested aspirin as a chemopreventive agent against breast cancer.[29] At the protein and mRNA levels, salicylate (an aspirin metabolite) was reported to be inhibitory on the cell growth and the syntheses of interleukin-6 (IL-6) and IL-11 in MDA-MB-231 and Hs578T cell lines, as is indomethacin, one of the NSAIDs.[29] The in vitro effects of salicylate were investigated on the breast cancer cell lines Hs578T, MCF-7, MDA-MB-231, and T-47D, indicating that it inhibits the breast tumor growth and disables breast cancer cells to some degree to induce osteoclast recruitment and osteolysis.[29]

Almost without affecting normal lymphocytes, sodium salicylate, JA, and MJ were shown to suppress the cell proliferation and trigger cell death in a range of cancer cell lines including Molt-4 (human T lymphoblastic leukemia), LNCaP (human prostate adenocarcinoma), MCF7 (human breast carcinoma), and SK28 (human melanoma).[1] After MJ was demonstrated to boost the survival of mice bearing EL-4 lymphoma, the cytotoxicity of sodium salicylate, JA, and MJ was comparatively studied by using the trypan blue exclusion method, indicating: (1) that sodium salicylate suppressed cell proliferation in all tested cell lines, (2) that JA brought about death in Molt-4 cells and caused proliferation suppression in the other cell lines, and (3) that MJ triggered the death of each tested cell line.[1] This study suggested that SA and other plant stress hormones might impact adversely on some cancer cells. As a matter of fact, SA participates in intracellular physiological and metabolic events characteristic of stress responses in mammalian cells, for instance, p38 MAPK activation,[30] in addition to affecting the stress-related transcription factors NF-κB and heat shock transcription factor (HSF).[31,32] Furthermore, SA and its acetate (viz., aspirin, an NSAID) can inhibit the synthesis of the human hormone PGs,[33] besides its subsequent recognition as a potent chemopreventative agent.[169,170] Strikingly, the chemopreventative activity of NSAIDs was thought to be ascribed to their tumor regressive properties in conjunction with their induction of differentiation and apoptosis.[35,36,136]

Although markedly different in inhibiting platelet aggregation, both sodium salicylate and aspirin were able to induce apoptosis and to activate caspases in myeloid leukemia cell lines and B-cell chronic lymphocytic leukemia cells.[171,172] Moreover, SA was demonstrated to enhance apoptosis in certain cell lines like human FS-4 fibroblast and pancreatic cancer via the p38 MAPK pathway.[30,173] This is reasonable since sodium salicylate and aspirin were both shown to inhibit the activation of the transcription factor NF-κB through the pathway activated by TNF and other agents, with the inhibitory effect of sodium salicylate being ascribed to its blockages of phosphorylation and subsequent degradation of IκB-α (an NF-κB inhibitor).[174,175] Furthermore, SA was shown to inhibit TNF-induced activation of Jun N-terminal kinase (JNK), a stress-activated protein kinase belonging to the MAPK family, whereas sodium salicylate treatment alone strongly activated p38 kinase to cause cell death via apoptosis as substantiated by the observation that SB-203580 (a validated p38 kinase inhibitor[176]) prevented salicylate-induced apoptosis.[30]

In addition to the aforementioned cellular apoptosis, other possible mechanisms underlying the antitumor action of SA and its analogues may involve inhibition of COX and DNA mismatch repair because highly complex processes exist certainly during the transformation of normal cells into cancer cells.[3,37] In spite of considerable achievements regarding the topic, the exact pathway whereby salicylates might affect carcinogenesis still awaits more in-depth investigations. However, the quantitative information concerning how they modulate the physiological and biochemical processes of plants would be essential for updating the current understandings about the key stages of cancer development, as well as for the subsequent efforts in preventing tumor progression through a skillful application of this type of stress-associated phytohormones and/or the analogues thereof.

3.2. Antimicrobial Activity

The human opportunistic pathogenic bacterium *Pseudomonas aeruginosa* is the major cause of chronic lung infections occurring frequently in patients who suffer from cystic fibrosis, burn injury, and other immunocompromised disorders, and its infection is now becoming more and more serious owing to its resistance to most of currently prescribable antibiotics.[177−179] Using *Arabidopsis thaliana*−*P. aeruginosa* and *Caenorhabiditis elegans*−*P. aeruginosa* pathosystems, the plant hormone SA was disclosed

to attenuate *P. aeruginosa* infectivity in both hosts by downregulating the production of a series of virulence factors and biofilm formation, rather than by inhibiting the bacterial growth.[40] This is in agreement with the previous observation that *P. aeruginosa*, along with several other Gram-negative bacteria, is capable of forming unique biofilms self-optimized via quorum sensing mechanism.[180] Thus, to conquer the multiple drug-resistant infections, it is necessary and urgent to develop novel strategies such as the establishment of therapeutics that may potentially disrupt biofilm formations, downregulate virulence factors, or modulate key genes governing pathogenesis and quorum sensing.[181−184] In spite of the host difference, the pathogenesis of *P. aeruginosa* was shown to require a similar array of virulence factors for both plant and animal infections,[185,186] suggesting the presence of some common components/targets in the eukaryotic immunity system against this pathogen. As reported by Prithiviraj et al,[40] SA serves as an anti-infective compound affecting the physiology of *P. aeruginosa* with the ultimate outcome of weakening its virulence besides the well-known role as a stress-responsive plant hormone. The evidence presented therein also demonstrated that SA selectively suppressed the transcription of exoproteins and of other virulence factors in *P. aeruginosa* without detectable effects on the expression of bacterial housekeeping genes.

In addition to their antibacterial activity, salicylates including sodium salicylate and aspirin were reported to be antiviral by inhibiting the replication of flaviviruses such as Japanese encephalitis virus and dengue virus.[41,42] As a valuable extension of the antiviral action of SA, aspirin was shown to be active against hepatitis C virus (HCV) by using an HCV subgenomic replicon cell culture system (referred to therein as Huh7 replicon cells).[43] The results showed that the aspirin administration disabled the viral replication because of the decreases in HCV-RNA and protein levels. Moreover, the anti-HCV action of aspirin in the Huh7 replicon cells was demonstrated to be attributable to its inhibition on COX-2 expression mediated partially through the activation of MEK1/2 (=MAPK/ERK1/2) and/or p38 MAPK pathways. Among so far identified COX enzyme isoforms, only COX-2 activation is implicated in HCV replication.[187] Accordingly, aspirin could be recommended as a potential adjuvant in the treatment of chronic HCV infection.

A recent study has shown that aspirin interrupts in vitro and in vivo replication of influenza virus jointly through impairing expressions of proapoptotic factors, suppressing caspase activation, and attenuating caspase-mediated nuclear export of viral ribonucleoproteins (RNP).[42] Moreover, the influenza virus propagation was indicated to depend on the function of the IKB kinase (IKK)/NF-κB module,[188] offering the spectacular probability to screen for the antiviral therapeutics targeting this cellular signaling pathway. As suggested earlier,[189] during antiviral prevention and therapy, an advantage of targeting some host cellular components over acting directly on the virus lies in the fact that the virus cannot survive in the impaired cellular microenvironment, or at least the occurrence of resistant viral variants should not be so frequent. These observations rationalized at least in part that the currently available SA-based aerosolic drugs may act as anti-influenza agents with the public acceptability and without inducing the resistant viral variants.

3.3. Neuroprotection against Prion-Related Diseases

Prions, infective particles composed primarily of proteins, is the cause of fatal neurodegenerative diseases occurring both in humans, as Kuru, CJD (Creutzfeldt−Jakob disease), FFI (fatal familial insomnia), and GSS (gerstamann Straussler Sheinker syndrome), and in animals as bovine spongiform encephalopathy and sheep/goat scrapie.[190] The pathogenicity of prions is known to arise from the conversion of the cellular isoform of prion protein (PrP^c) to the pathogenic isoform (PrP^{Sc}) with a high percentage of β-sheet secondary structure in comparison to PrP^c, which in turn facilitates the formation of the proteolysis-resistant amyloid fibrils injuring and/or degenerating neural tissues. To aid the related research, PrP106-126, a kind of synthetic prion fragment consisting of amino acid residues 106-126 near the N-terminal of the human prion, can be used alternatively for studying the pathogenesis of PrP^{Sc}, because PrP106-126 possesses many properties of the entire PrP^{Sc} and has been proven to accumulate fibrils that damage neurons either directly (by interacting with components of the cell surface to trigger cell apoptosis signaling) or indirectly (by activating microglia to produce inflammatory mediators).[191] This is in accord with the observation that neuron degeneration is boosted by coculturing with activated microglia to release pro-inflammatory cytokines TNF-α and IL-1β,[192,193] whose expressions are coregulated by the transcription factor NF-κB with its binding sites in the promoter region of the gene serving as inducible transcriptional regulatory elements.[194−197] Recently, aspirin was shown to inhibit the cell death triggered by PrP106-126 peptide as evidenced from the observation that the number of apoptotic neuro-2a cells after treatment with 5 mM aspirin was ~3 times lower than that of the untreated control. Moreover, the treatment of microglia with PrP106-126 was demonstrated to upregulate the expression of pro-inflammatory cytokines TNF-α and IL-1β in a time-dependent manner.[198]

Aspirin was ascertained to block NF-κB activation in rat neuronal cultures, and its anti-inflammatory effects are partially mediated through its specific inhibition of IKK-b, thereby blocking inflammation-associated genes that are activated by NF-κB.[38,39] These findings support the suppressive effects of aspirin on PrP106-126-induced apoptosis of neuro-2a cells cocultured with rat microglia cells.[198] Although little convincing data is currently available for managing prion protein diseases, the investigation suggests that the suppression of NF-κB-activated pathway in microglia cells may mitigate the progression of inflammation and neuronal degeneration in prion diseases.[198]

Overall, the knowledge regarding the effects of those cytokines produced by microglia upon exposure to PrP^{Sc} is spare, and the mechanisms by which microglia mediate neuronal cell damage remain elusive. However, the aforementioned evidence concerning aspirin is promising and valuable in mankind's combat with the prion-associated neural degenerative disorders such as Alzheimer's disease.[199]

3.4. Functional Scaffold Analysis

As mentioned in section 2.4, a variety of cellular processes in mammals are affected by the AKR superfamily including four human hydroxysteroid dehydrogenases (HSDs), referring to as AKR1C1 (20α-HSD), AKR1C2 (type 3 3α-HSD), AKR1C3 (type 2 3α-HSD), and AKR1C4 (type 1 3α-HSD). Biochemically, these four isoforms of AKR1C share at least 86% sequence similarity, with AKR1C1 and AKR1C2 differing in only seven amino acid residues. Concerning the function, the isoform AKR1C1 plays multiple roles in mammalian cells including mainly: (1) the involvement in progesterone metabolism for the maintenance of pregnancy,[200] (2) the linkage with symptoms of

premenstrual syndrome and other neurological diseases due to the elimination of neuroactive steroids metabolized by 20α-HSD enzyme into inactive 20α-hydroxysteroids,[201−203] and (3) the implication in the development of mammalian tumors including lung, endometrial, esophageal, ovarian, and breast cancers. In addition, the AKR1C1 overexpression in cancer cells is associated with the drug-resistance to some chemotherapeutic agents.[204−208]

Because the overexpression of AKR1C1 is involved both in the pregnancy termination and in the development of hormone-dependent endometriosis syndrome as well as endometrial and breast cancers, the AKR1C1 inhibitors could be promising agents for lessening or eliminating the risks of premature birth, as well as for treating neurological disorders and gynecologic cancers.[209] Among the well-documented AKR1C1 inhibitors are NSAIDs, bile acids, phytoestrogens, synthetic estrogens, and benzodiazepines, in addition to a group of newly synthesized SA-inspired chemicals, some of which showed IC_{50} or K_i values in the micromolar range toward the AKR1C1 enzyme.[210] Among them, benzbromarone and 3′,3″,5′,5″-tetrabromophenolphthalein (Figure 4) were the most potent inhibitors with IC_{50} values below 50 nM (48 and 33 nM, respectively).[202] Aided by the active site recognition via crystallographic approach, 3,5-dichlorosalicylic acid, a more potent SA-based AKR1C1 inhibitor, was screened out with a K_i value of 6 nM.[209,211] Moreover, the selectivity of 3,5-dichlorosalicylic acid was probed because it displayed much more potent inhibitions toward AKR1C1 and AKR1C2 enzymes than toward the isoforms AKR1C3 and AKR1C4. The high selectivity and analogous efficacy in the inhibition on AKR1C1 and AKR1C2 are considered to be ascribed to the structural similarity of their active sites differing in only one amino acid residue, namely, Leu54 in AKR1C1 and Val 54 in AKR1C2.[211] According to the above findings and an earlier analysis of inhibitor-binding site,[212] El-Kabbani and coworkers predicted that the replacement with a phenyl of the 5-bromine atom of 3,5-dibromosalicylic acid would promote the inhibition efficacy and selectivity toward AKR1C1 over AKR1C2. This presumption was followed by the experimentation leading to the discovery of 3-bromo-5-phenylsalicylic acid with twofold more inhibitory potency as well as selectivity toward AKR1C1 over AKR1C2 in comparison to 3,5-dibromosalicylic acid.[210] In addition, a library of 250 000 chemicals from the NCI database was screened previously for AKR1C1 inhibitors, based on their chemical complementation and steric compatibility with enzyme active sites. As a result, 3,5-diiodosalicylic acid (an SA analogue) was demonstrated as a potent competitive inhibitor with a K_i value of 9 nM, in contrast to the characterization of SA and aspirin as AKR1C1 inhibitors with IC_{50} values of 7.8 and 21 μM, respectively.[209]

AKR1C3 that is expressed in the prostate and breast tissues can catalyze the reductions of androstenedione and estrone into their more active forms, testosterone and 17β-estradiol, respectively. Therefore, AKR1C3 may be an effective target for developing drugs for the prevention and treatment of the hormone-dependent carcinoma including prostate, endometrial, and breast cancers. Functioning as a PGF synthase, AKR1C3 is also involved in PG signaling to convert PGD_2 into $PGF_{2\alpha}$, thus preventing the spontaneous generation of $15dPGJ_2$, a natural activating ligand for PPARγ. Accordingly, AKR1C3 is also recognized as a potential cellular target for cancer prevention and therapy based on its blocking the cell differentiation through indirect antagonism of PPARγ,[213] because the activation of PPARγ receptor may induce cell differentiation and lead to apoptosis in many neoplastic cell lines.[118,145,214] Consequently, AKR1C3 inhibitors are of value in the development of therapeutic agents against both hormone-dependent and -independent cancers.

N-Phenylanthranilic acid and derivatives are well accepted as nonspecific inhibitors of all AKR1Cs in spite of their higher potency for inhibiting AKR1C1 and AKR1C2 with the IC_{50} values comparable to those of mefenamic acid, a prescribed anti-inflammatory drug.[215] The SA-based inhibitors of AKR1Cs are an important reservoir where the starting molecule can be extracted for the exploration and development of AKR1C1 inhibitors with the desired selectivity. Interestingly, originating from a couple of bioisosteres, anthranilic and salicylic acids, two typical classes of NSAIDs known chemically as mefenamic and acetylsalicylic acids were discovered.[216] As proposed earlier by Thornber,[217] the term bioisosteres is defined in a broad sense as subunits or groups or molecules possessing physicochemical properties of similar biological effects. As a driving strategy of molecular modification, the bioisosterism exhibits its unique significance in constructing a new series of congeners, out of which novel drug candidates could be explored.[216]

4. AUXIN

Auxin plays important roles in regulating plant development and physiology including embryogenesis, vascular differentiation, organogenesis, tropic growth, and root and shoot architecture.[50,51] As an important auxin, indole acetic acid (IAA) is believed to be synthesized in plants and to affect a variety of key processes even at a picomolar concentration. Accumulating evidence has indicated that IAA can also be produced by some microorganisms such as fungus[218] and animals including mammals.[219−221] In animals, IAA could be originated from the intestinal uptake of a vegetable-rich diet after ingestion and/or be synthesized from tryptophan, the ubiquitous precursor for IAA biosynthesis in plant and animal tissues.[222] Furthermore, IAA is detectable in human urine, blood plasma, and the central nervous system.[219−221] The distribution of IAA in nonplant organisms could be an acceptable embodiment of its cross-kingdom actions as mentioned below.

4.1. Medical Functions of IAA

4.1.1. Antitumor Action. IAA alone is not substantially cytotoxic, whereas it can be converted into the active form after oxidative decarboxylation by horseradish peroxidase (HRP).[4] More recent studies have confirmed that IAA in combination with HRP induces the apoptosis of G361 human melanoma cells. This led to a postulation that hydrogen peroxide (H_2O_2) could be a major mediator of IAA/HRP-induced apoptosis that can be blocked by catalase,[52] as well as by the caspase-8 inhibitor z-IETD-FMK (benzyloxycarbonyl-Ile-Glu-Thr-Asp(OMe)-fluoromethyl ketone). This reinforced the involvement of caspase-8 in the aforementioned observation.[53] Furthermore, IAA/HRP-induced apoptosis was shown to proceed through a CD95-initiated death receptor signaling pathway triggered by H_2O_2.[53]

Biochemically, HRP is present in the ferric form as a heme-containing peroxidase enzyme in its native state. It oxidizes a magnitude of substrates in the presence of hydrogen peroxide through catalyzing one-electron oxidation reactions via its complex I and II forms (Figure 5), and IAA can be in vitro metabolized by peroxidase or by rat neutrophil homogenates to release ROS.[223,224] Accordingly, it is not surprising that IAA

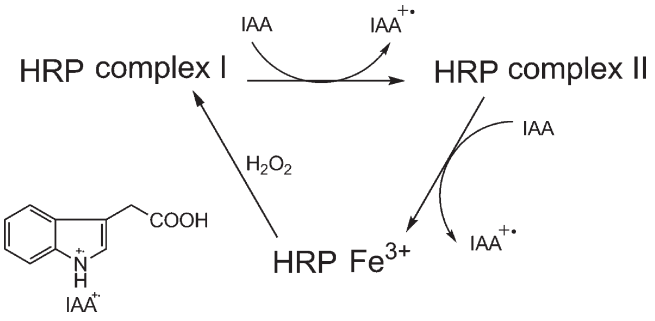

Figure 5. HRP transformation among its native ferric, complex I, and complex II forms.

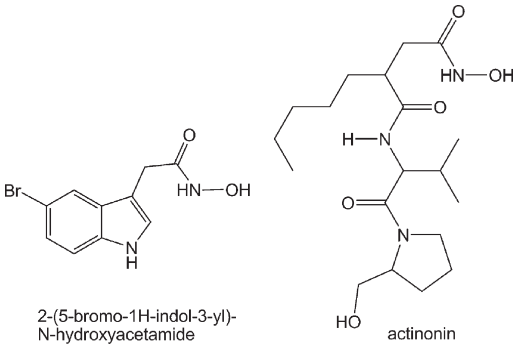

Figure 6. Structures of 2-(5-bromo-1H-indol-3-yl)-*N*-hydroxyacetamide and actinonin. Although sharing an *N*-hydroxyacetamide side chain, the former is a selective bacterial PDF inhibitor whereas the latter inhibits both human and bacterial PDF.

and its synthetic derivatives could be oxidized by HRP to form cytotoxic species such as indolyl radical cation ($IAA^{+\cdot}$), which is valuable for the discovery of novel cancer therapeutic agents.[4] Moreover, the HRP-catalyzed oxidation of IAA produces a mammalian cytotoxin that can damage plasmid DNA,[4] explaining as well its inhibitory effects on bacterial growth. The low toxicity of IAA and its tolerance to endogenous mammalian peroxidases raise collectively a possibility for its utilization in a HRP-directed antitumor prodrug therapy, which is unique in the production of toxic IAA metabolites like $IAA^{+\cdot}$ exclusively within the tumor tissue without affecting normal tissues.[225]

As reviewed by Folkes and Wardman,[4] 3-methylene-2-oxindole generated further from $IAA^{+\cdot}$ via a 5-step reaction also contributes to the cytotoxic effect of the IAA/HRP combination because it can bind to DNA bases and protein thiols. On the basis of the findings, some cytotoxic IAA derivatives were synthesized. However, the exact structure−activity relationship remains elusive.[4] Still under exploration is the investigation aiming at successful applications of antibodies, polymers, and genes as carriers for IAA/HRP-based and cancer-targeting drug delivery system,[225] and the gene-directed-enzyme-prodrug therapy (GDEPT) merits attention as well. The *hrp* gene, deliverable technically to the cancer cell by viral or nonviral carriers, can be expressed at the target site to produce HRP enzyme that subsequently catalyzes a prodrug to form a toxic agent. As the first step, the *hrp* gene has been sequenced, documented, and expressed as desired in bacterial (*Escherichia coli*)[226] and mammalian cells.[227,228] As a confirmation to the feasibility of the IAA/HRP GDEPT approach, the transfection of human bladder cancer cell line T24 with *hrp* gene resulted in a decreased colony formation upon IAA exposure as compared with untransfected cells.[228]

On the other hand, the antitumor action of IAA may be allowed alternatively through its antioxidant activity. For example, the hepatoprotective effects of IAA against induced carcinoma have recently been reported by using a diethylnitrosamine (DEN)-induced hepatocarcinoma mouse model.[229] The prophylactic function of many compounds has been linked to the antioxidant action as evidenced from the discerned ROS depletion,[230] because the accumulation of intracellular ROS during continual oxidative stress contributes substantially to the development of various chronic diseases including liver disorders and cancers.[231] However, the intracellular ROS levels are strictly controlled by the cellular mechanisms involving the homeostasis of oxidant and antioxidant molecules, which is in turn mediated by regulatory enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) and/or by antioxidant compounds like glutathione, ubiquinone, flavonoids, vitamins (A, E, and C), etc.[232] These enzymes SOD, CAT, GPx, and GR are known as sensitive indicators of elevated oxidative stress, and the increases in their activities are results of protective responses to scavenge ROS.[233,234] On the basis of the experimentation in mice with DEN-induced hepatocarcinoma, the protective action of IAA against hepatocarcinogenesis was demonstrated for the first time by means of a DEN-protective effect (reflected by CAT and GR activities), as well as by affecting antioxidant gene expression and DNA fragmentation.[229]

4.1.2. Antimicrobial Activity of Indole Derivatives. An indole-based derivative, 2-(5-bromo-1*H*-indol-3-yl)-*N*-hydroxyacetamide (Figure 6), has been recently identified as a potent inhibitor of bacterial peptide deformylase (PDF) without affecting human mitochondrial PDF (mPDF), thereby avoiding adverse effects on normal human cells.[56] This indole derivative is obviously advantagous over actinonin that, though prescribed as an antibiotic in clinic, has been demonstrated to be cytotoxic toward some cell lines through inducing apoptosis. PDF was originally identified as a specific bacterial target for screening the new antibiotics against the multidrug-resistant pathogenic bacteria, the main cause of serious human infections for decades. Aided by the recent finding of a human homologue of mPDF whose inhibition causes cell death,[235−237] a new scaffold has been explored to discriminate between human and bacterial PDFs.[56] A skillful combination of medium-throughput NMR screening and SAR analysis was applied to search for suitable compounds that would bind to bacterial PDF (two distinguished types: PDF1B and PDF2) but not to mPDF, and finally the indole scaffold was selected.[56] Through further modification at C3 and acetamide group of 5-bromated IAA, 2-(5-bromo-1*H*-indol-3-yl)-*N*-hydroxyacetamide (Figure 6) was obtained with the best inhibitory selectivity between bacterial and human PDFs. This compound inhibited discriminatively bacterial PDF2 and mPDF with the IC_{50} values of 0.01 and 130 μM, respectively, in contrast to those (0.01 and 0.03 μM) of actinonin coassayed in that study.[56] It is noteworthy that the indole moiety was shown by SAR analysis to bind to both PDF1B and PDF2,[56] suggesting that the indole scaffold can be of significance in the design and development of new antibiotics that are expected to display high selectivity toward bacteria, thereby facilitating our battle against the emerged and emerging pathogens with the multidrug resistance.

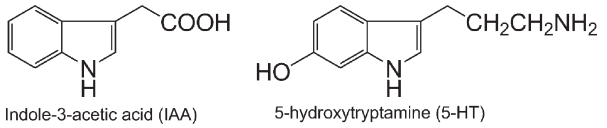

Figure 7. Structures of IAA (a plant auxin) and 5-HT (a mammalian neurotransmitter).

4.2. Serotonin and IAA

The above-described bromo-substituted indole−hydroxyacetamide is reminiscent of the well-known mammalian neurotransmitter 5-hydroxytryptamine (5-HT), commonly called serotonin (Figure 7). Also impressive are its structural homology to IAA and its production by some microbes.[54]

Besides its ubiquity in mammals, 5-HT is also found in some plant tissue such as fruits and seeds and demonstrated to be involved in promoting the stem growth and attenuating leaf senescence in higher plants.[55] In all cases, 5-HT is generated from tryptophan (Trp) but through different metabolic paths. In plants 5-HT is produced through the decarboxylation of Trp into tryptamine in the presence of Trp decarboxylase, followed by hydroxylation catalyzed by tryptamine 5-hydroxylase.[55] In mammalian cells, it is formed through sequential hydroxylation by Trp hydroxylase and decarboxylation by 5-OH Trp decarboxylase.[238] However, the microbial production of 5-HT remains elusive, although previous experimentation with the yeast *Candida guilliermondii* detected the presence of Trp hydroxylase. The subsequent observation concerning the suppression of 5-HT formation by a Trp hydroxylase inhibitor *p*-chlorophenylalanine suggested that the operation for 5-HT in the microorganism most likely followed its animal-type biosynthetic path.[239] Moreover, *p*-chlorophenylalanine did not affect the growth dynamics of *Escherichia coli*, implying that a plant-type biosynthetic pathway for 5-HT independent of any Trp hydroxylase might be present in this bacterium.[240] The observations highlighted that the fungus and bacterium, if they do, probably synthesize 5-HT differently. Another interesting aspect in the 5-HT metabolism is that it can be hydroxylated in mammals by monoamine oxidase to yield 5-hydroxyindoleacetic acid, which can also be produced by certain bacteria.[54] In addition to its indispensable action in mammals, 5-HT seems to be an important plant growth regulator as well,[55] although its impact on microbes and symbiotic system consisting of ascrid and *E. coli* in host animal intestine needs to be clarified further.[238]

4.3. Modulator of Plant−Bacteria Interaction

The wide distribution of IAA in plants and microbes suggested its possible involvement in plant−microbe interactions. As reviewed by Spaepen et al.,[241] several biosynthetic pathways of IAA in plant-associated bacteria have been identified, indicating a high degree of similarity in IAA biosynthesis between plants and bacteria. Again, Trp has been characterized as a main precursor of IAA in the bacteria, and five different pathways starting from Trp are present in plant-associated bacteria, among which the key genes involved in the IAM (indole-3-acetamide) and IPyA (indole-3-pyruvate) pathways are distributed in the genomes of sequenced microorganisms. Concerning the best investigated IAM pathway, the genes *iaaM* and *iaaH* that encode the enzymes for the conversion of Trp into IAA via IAM have been cloned and characterized from a spectrum of bacteria as represented by *Agrobacterium tumefaciens*, *Pseudomonas syringae*, *Pantoea agglomerans*, *Rhizobium*, and *Bradyrhizobium*.[242−245] Molecular analyses regarding the bacterial IAA biosynthetic pathway and the modulation thereof have suggested the possible outcomes of the interactions between plants and IAA-producing bacteria, varying from phytopathogenesis to plant growth promotion. It is proposed that phytopathogenic microbes tend to use the IAM pathway to produce IAA whereas plant-beneficial bacteria prefer to take the IPyA pathway.[241]

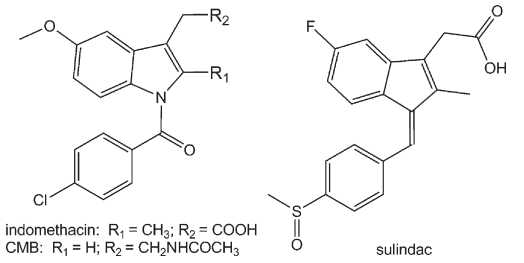

Figure 8. Bioisosteric relation among indomethacin, CMB, and sulindac.

4.4. Indole and Its Lookalike Scaffolds

Indomethacin has been accepted as the best compound in terms of its preferential inhibition on AKR1C3 over the other AKR1C isoforms among the aforementioned NSAIDs.[246] Since its approval in 1965, indomethacin has been frequently prescribed to reduce fever, pain, stiffness and swelling owing to its inhibition on PG productions. Among the indomethacin analogues in clinical use, sulindac is a representative example. Viewed from the structural aspect, bioisosteric relation exists between sulindac and indomethacin, with the latter containing an IAA core and the former contianing an isostere thereof (Figure 8).

Lightened by the observation, an indomethacin analogue *N*-(4-chlorobenzoyl)melatonin (CBM, Figure 8) was identified as a specific inhibitor of AKR1C3, thereby becoming a promising drug candidate for treating hormone-dependent and -independent breast cancers.[247] The SAR strategy was adopted to guide the development of the indomethacin-related AKR1C inhibitors selectively acting on AKR1C3 without affecting two other isoforms, AKR1C1 and AKR1C2. Moreover, the crystal structure of the AKR1C3·$NADP^+$·indomethacin complex provided an ideal model for exploring the structural mechanism for the inhibition of AKR1C3 enzyme. Through the crystallographic analysis, the acetic acid group of indomethacin was found to extend into the similar subpocket of AKR1C3 as does flufenamic acid, which is another prescribed NSAID drug additionally with the COX enzyme inhibitory activity.[247,248] These findings suggest that the substitution pattern on the indole core impacts the selectivity toward the inhibition of AKR1C3 versus AKR1C2, with the concomitant consequence of lowered or deprived inhibitions on PGHS-1 and PGHS-2. Furthermore, the research group found that indomethacin and its methyl ester were highly specific for the AKR1C3 inhibition over the other AKR1C isoforms.[246] After scrutinizing the crystal structure of AKR1C3 and experimental observations with indomethacin and its derivatives, it was concluded that CBM, a close relative of indomethacin (Figure 8), was a specific AKR1C3 inhibitor, which was unable to inhibit COX-1 and COX-2.[249] Quantitatively, CBM was disclosed to inhibit in an uncompetitive manner AKR1C3 using 9,10-phenanthrenequinone as the substrate with a K_i value of 3.4 μM, whereas AKR1C1 and AKR1C2 were almost unaffected even at 60 μM.[247] Therefore, the indole scaffold (shared by IAA and 5-HT) and its "look-alike" (as constructed in sulindac), along

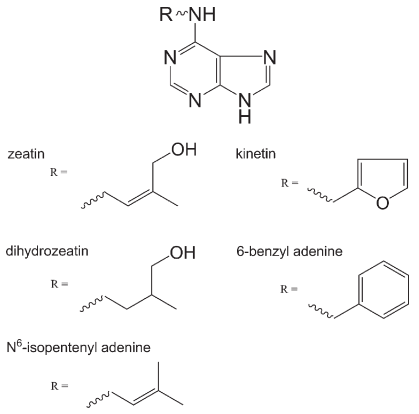

Figure 9. Structures of some naturally occurring CTKs.

with its substitution pattern, contributes substantially to the pharmaceutical effects of indomethacin and its analogues such as CBM and sulindac (Figure 8).

5. CYTOKININ

Cytokinin (CTK) is a category of adenine-derived signaling molecules, constituting the five families of "classical" phytohormones together with auxin, gibberellin (GA), abscisic acid (ABA), and ethylene. In the mid-1960s, it was noticed that a small molecule degraded from DNA could stimulate the growth of plant tissues in vitro.[250] This substance was named kinetin, belonging to the class of regulators called CTKs.

Literally, cytokinin (CTK) means stimulus of cell movement (cytokinesis), but it covers cell division as well. CTKs can induce callus to redifferentiate into adventitious buds besides promoting cell division and regulating a variety of developmental process in plants such as apical dominance, seed germination, de-etiolation, leaf senescence, nutrient mobilization, and plant−pathogen interaction.[59,60] A plant callus is an undifferentiated cell mass that is immortal and proliferates indefinitely in a disorganized manner, resembling biologically some human cancer cells.[74] Presumably because of the close similarity in the biological phenotypes between the mammalian cancer and plant callus cells, CTKs may affect the differentiation of human cancer cells through the mechanism by which they modulate a set of biological processes in plants.[61] The naturally occurring CTKs are structurally so diverse that they are divided into three groups: isoprenoid CTKs (zeatin and its dihydro-derivatives, isopentenyladenine), aromatic CTKs (benzyladenine, methoxytopolin), and furfural derivatives (kinetin and kinetin riboside, KR) (Figure 9).[251] CTKs, specifically N^6-isopentenyladenosine (i^6A), occur usually as a bound form in the tRNA of many eukaryotic and prokaryotic cells, although larger amounts of free CTKs are found in plant cells. Among the free CTKs, the isoprenylated ones are the most abundant, and adenine derivatives with aromatic substitution are also present in some plant species. Moreover, the *O*-glucosyl-conjugation at the N^6-side chain is a common modification in plants since *O*-glycosylated CTKs are inert to CTK oxidases that catalyze the cleavage at the N^6-side chain to generate adenine and the other moiety. In plants, the glycosylated CTKs are the store form of these phytohormones, which, if necessary, can be transported safely into specific organs. Interestingly, it is noteworthy that free (not bound to tRNA) i^6A was detected in cell extracts of some yeasts such as *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*.[252]

The aforementioned inherent association of DNA and RNA may foretell the cross-kingdom action of these phytohormones, as exemplified below.

5.1. Antitumor Activity

Although the biological functions of CTKs in plants have been widely investigated, little is known so far concerning the mechanism of their roles in mammalian and microbial cells. The apoptosis-inducing activities of CTKs have been discerned in some cancer cell lines such as Hela and mouse melanoma B16 F-10 cells.[253] For example, kinetin riboside (KR), a CTK analogue, induces apoptosis by disrupting the mitochondrial membrane potential, thus releasing cytochrome c and activating caspase-3 via the modulation of Bcl-2 family proteins. The Bcl-2 family proteins play important roles in apoptosis, and the interactions between the antiapoptotic and proapoptotic members provide a mechanistic basis in regulating the apoptotic cell death.[254,255] Some antisense oligonucleotides targeting Bcl-2, along with other small-molecule inhibitors of Bcl-2 and Bcl-X_L, can result in elevated tumor cell apoptosis, suggesting that the inhibition of the antiapoptotic proteins might be an intriguing strategy for selective killing of malignant tumor cells. Recent findings about CTKs and cancer cells indicated that KR induced mitochondrial membrane disruption via the downregulation of the antiapoptotic proteins Bcl-2 and Bcl-X_L, which led to the caspase-3 activation and ultimately the programmed cell death (= apoptosis) in cancer cells.[253]

N^6-isopentenyladenosine (i^6A), an N^6-isopentenylated nucleoside, was detected earlier in the mammalian cytoplasm.[256] After being recognized as a potential therapeutic agent for some epithelial cancers,[257] the gene toward which i^6A may target was explored, together with the preliminary understanding of its structure−activity relationship (SAR) concerning this type of antitumor compound.[258] As the only known CTK existing in animal tRNAs,[259] i^6A was found to play a predominant role in posttranscriptional processes including the function of mammalian selenocysteine tRNA. When bound to tRNA, i^6A may participate in the improvement of reading frame maintenance,[260] whereas the absence of i^6A in selenocysteine tRNA may inhibit selenoprotein synthesis.[261] Furthermore, i^6A was shown to have pleiotropic effects on mammalian cell cytoskeleton, proliferation, and apoptosis, possibly due to its associations with isoprenoid metabolism and its direct biological activities.[61] When taking into account preliminary clinical surveys on its therapeutic use, i^6A may be recommended as a promising antitumor agent.[61]

For this reason, the evidence concerning in vivo efficacy and mechanism (or mode of action) of i^6A is piling up quickly. In addition to its inhibitory effects on mammalian leukemia cells, recent experimentations with nine human epithelial cancer cell lines derived from different types of malignant tissue afforded the complete suppression of clonogenic activity in 8 of the 9 cancer cell lines upon i^6A administration. It is therefore proposed that the tumor-inhibitory activity of i^6A may be ascribed to the suppression of cell proliferation, the disturbance of DNA synthesis, and morphological alterations.[257] Moreover, the antiproliferative effect of i^6A was confirmed in vivo in a nude mouse xenograft model by a drastic reduction in tumor volume upon its treatment.[262]

The isopentenyl transferases (IPTs), ubiquitous as evolutionarily conserved proteins in the eukaryotes ranging from yeast to mammals, can catalyze the addition of i^6A on residue 37 of tRNA.[263] In plants, some of the IPT-related proteins function as

tRNA-IPT and others are involved in the synthesis of free i^6A or its relatives such as CTKs that influence the growth, development, and other physiological processes.[59] The human tRNA-IPT-1 protein (E.C.2.5.1.8), an enzyme catalyzing the transfer of an isopentenyl group from isopentenyl diphosphate to the preformed tRNA, is encoded by the tRNA-IPT-1 (*TRIT1*) gene that was found to be a tumor-suppressor gene in lung cancer.[259] The human *TRIT1* gene in the oncogene MYCL1 locus has been evidenced to be pivotal in the control of tumor progression.[264] Also interesting is the high homology of the human IPT in amino acid sequences with the IPT proteins produced by *Saccharomyces cerevisiae* and *Escherichia coli*.

As a hot topic in cancer therapy, i^6A was shown to induce the human leukemia cell differentiation[129] and to inhibit the proliferation of a K-*ras*-transformed rat thyroid cell line.[262] This is in accord with its antileukemic activity against a mouse leukemia cell line.[265] Recently, i^6A was also demonstrated to be antiproliferative and apoptosis-inducing in human colon cancer cells,[266] suggesting its potential antitumor effects against a variety of mammalian cancers. These findings would motivate further studies on the i^6A analogues with superior antitumor activities and improved stability in plasma. Additionally, new drug delivery systems that direct i^6A or its antitumor analogues to the target cancer tissues would be expected to exert better therapeutic efficacy with negligible or minimal side effects.

In the early 1970s, several putative mechanisms underlying the actions of i^6A were proposed, mainly including the cell proliferation inhibition, protein prenylation blockage, apoptosis induction, and suppressions of DNA/RNA/protein synthesis and nucleoside transport.[267,268] However, not as quick as desired was the progress in the elucidation of the precise mechanism concerning how i^6A functions to suppress cancer cell proliferation. Recently, the gene expression profiling studies of i^6A-treated cells have demonstrated that induction of such genes as *PPP1R15A*, *DNAJB9*, *DDIT3*, and *HBP1* is involved in the downregulation of cell cycle progression and the upregulation during cell cycle arrest under the stress conditions.[258] The microarray analysis data revealed the modulation of over 110 genes at the sixth hour post i^6A treatment. The expression profiling analysis over different time points indicated that early modulated genes in response to i^6A include those associated with the transcriptional regulation, which subsequently activate and/or suppress other cell cycle- and/or apoptosis-related genes.[258] The unfolded proteins may be refolded in a correct manner by chaperone proteins or degraded via the ubiquitin-proteasome pathway; otherwise, cells would die because the misfolded proteins are exceeding.[269] It is therefore noteworthy that the modulation of gene *DDIT3* affects "unfolded protein response", highlighting that i^6A may maintain proteins in the unfolded (correct) form in response to cellular stress stimuli.[258] In spite of accumulating evidence for antitumor effects of i^6A in mammalian cells, the current knowledge about the SAR of CTKs and related mechanisms is limited on the whole. Recent research has been conducted to investigate inhibitory effects of several chemically synthesized i^6A analogues on cell proliferation.[258] The experimentation indicated that those analogues exhibited weaker or no inhibitions on the clonogenicity of A549 cells, suggesting that the ribose moiety thereof is necessary for the action toward the epithelial cancer cell growth. This pharmacogenomics study of i^6A supported as well the presumption that the anticancer mechanism of i^6A might involve the induction of cellular stress to generate cell cycle arrest and cell death. From the observation that the synthesized analogues of i^6A were less effective than i^6A or even ineffective against cancer, the high structural requirements of i^6A and its derivatives for the antitumor activity could be primarily figured out to be associated with the conformation, the copresence, and the combination of essential groups including ribose moiety, carbon−carbon double bond, etc. It awaits in-depth studies to find novel i^6A derivatives with more potency against tumor tissues, with less or no toxicity to the normal tissues and with improved stability in plasma.

5.2. Function in Rhizobium−Legume Symbiosis

A number of plant species have evolved an intimate association with nitrogen-fixing rhizobial bacteria that are typical of absorbing nitrogen from the environment to benefit their hosts. Central to this plant−bacterial symbiosis is the formation of "nodules" on plant roots following plant perception and recognition of rhizobial bacteria, which is defined as organogenesis.[270] It has long been recognized that CTKs are important for nodule initiation and development, and the initial evidence can be traced back to an earlier observation that rhizobial bacteria, such as *Rhizobium leguminosarum* and *Bradyrhizobium japonicum*, were able to secrete CTK-like compounds that could affect root development.[63,64] The CTKs' key roles in nodulation were disclosed by the fact that the transfer of the CTK production allows normally nonsymbiotic bacteria to activate nodule formation in alfalfa.[65] More recently, the localized production of CTKs in epidermis following nodulation (Nod) factor perception was shown to "orchestrate" epidermal and cortical responses during nodule formation, where Nod factor is known as lipochitooligosaccharide signals produced by rhizobia. CTKs are subsequently transported across the cells (probably by active transport) to the cortex, which initiates cell division followed ultimately by the formation of the nodule primordium.[66,67] Although CTKs are believed to play central roles in the symbiotic nodule differentiation, cortical cell division, and the induction of some Nod factor-dependent pathways, some questions such as how CTKs induce cortical cell division remain elusive. This pending problem was resolved partially by the finding that a D-type cyclin component of a kinase complex (CycD3), essential for the transition from G1- to S-phase in the cell cycle, mediates some of the effects of CTKs on cell proliferation in *Arabidopsis*.[271]

In addition to their key role in initiating the nodule primordium in the root cortex, CTKs might also govern the root epidermal susceptibility to rhizobial infection through mediating nodule inception (NIN) gene expression, as evidenced from the discerned colocalization of NIN and CTK in the epidermis in response to rhizobia, and from the observation that transcription of *pro*NIN:GUS [constructed by the fusion of promoter of *Lotus japonicus* NIN gene to a β-glucuronidase (GUS) reporter gene] is visible in the epidermis and root hairs upon rhizobial inoculation and/or Nod factor treatment.[272] As a matter of fact, NIN is essential in the epidermis to the formation of infection thread and bacterial entry.[273,274] Mounting data have unequivocally indicated that CTKs can also affect rhizobial infection by controlling the expressions of NIN and other transcriptional regulators through local and systemic regulatory mechanisms.[275]

5.3. Action in Phytopathogen Virulence

Many plant-associated bacteria interact with their hosts either by influencing the phytohormone production or by producing plant hormones themselves. They take such strategy to achieve advantages over their host plants, including enhanced nutrient release, suppression of host defense, and disease

establishment.[54,276] For example, gall-inducing bacteria like *Pantoea agglomerans* and *Pseudomonas syringae* subsp. *savastanoi* secrete high levels of CTKs and auxins to initiate gall development.[68,69] Another interesting exemplification of the topic is *Agrobacterium tumefaciens*, which can transform genetically plant cells via Ti-plasmid to convert them into CTK and auxin manufacturers.[277]

Plant pathogenic actinomycetes *Rhodococcus* and *Streptomyces* have vast host ranges including model plants and crops of economic importance.[278] This is particularly exemplified by *R. fascians*, which infects many monocot and dicot hosts.[279] The *R. fascians*-associated symptoms including leaf deformation, witches' broom, and leafy galls are generated by hyperinduction of shoots through activated formations of dormant axillary and de novo meristems. These disease symptoms are thought to result from the disturbance of the endogenous hormone homeostasis in the host plant by *R. fascians* that can degrade CTK and synthesize IAA mainly through IPyA pathway, leading to the alteration of the original or correct CTK/auxin ratio.[280,281] All deleterious effects associated with *R. fascians* infection are dependent not on plant cell transformation but on the expression of virulence-related genes of the bacterium and on the production of compounds that interfere with normal plant growth and development. The complexity of symptom development is further demonstrated by the necessary and continuous presence of the bacteria for the symptom maintenance.[279] The *R. fascians* virulence is controlled by genes on a plasmid, and three loci *fas*, *att*, and *hyp* on this linear plasmid have been identified.[70−72] Evidenced from the observation that deletions of some *fas* genes confer a nonvirulent phenotype, the *fas* operon is thought to be essential to *R. fascians* virulence.[72] Moreover, one of the genes within the *fas* operon has been disclosed to encode an IPT responsible for CTK biosynthesis like IPTs from *Agrobacterium tumefaciens* and *Pseudomonas syringae pv savastanoi*.[73]

Recently, three typical CTKs, isopentenyladenine, *trans*-zeatin, and *cis*-zeatin and their 2-methylthio (2MeS)-derivatives, were identified by CTK profiling of both the virulent *R. fascians* strain D188 and its nonvirulent plasmid-free variant D188-5.[282] The CTK levels in strain D188 are much higher than those in its nonvirulent counterpart, confirming that the linear plasmid is associated with the virulence production. Furthermore, all bacterial CTKs exhibiting synergistic effects in several bioassays could be perceived by two CTK receptors (AHK3 and AHK4) of the host plant. In addition, the *cis*- and 2MeS-derivatives were shown to be inert to the apoplastic CTK oxidase/dehydrogenase, with the latter displaying no cytotoxicity at high concentrations, suggesting that these bacterial CTKs are indispensable for the persistent tissue proliferation and the maintenance of hosts' disease symptoms.[282] This can be substantiated by an earlier finding that *R. fascians* induces the formation of differentiated leafy galls as indicated by numerous lateral embryonic buds in the axils of primordial leaf resulting from the outgrowth suppression, whereas no differentiated galls can be observed if provoked by such bacteria as *Pantoea agglomerans* and *Pseudomonas savastano*.[279] The *fas* operon in *R. fascians* is an excellent example of a highly regulated pathway required for its virulence and the generation of a modified array of CTKs. Surprisingly, the *fas* operon is also detected in the pathogenicity island (PAI) of *Streptomyces turgidiscabies,* the only other bacterial species capable of inducing differentiated leafy galls in aerial plant parts, which has been proven to result from the acquisition of a *R. fascians*-like *fas* gene.[283]

As reported earlier,[284,285] the nodulating rhizobia can produce CTKs with the related genes (homologous to the *A. tumefaciens IPT* gene) found in the rhizobial bacteria *Sinorhizobium meliloti* and *Mesorhizobium loti.* As accepted, *A. tumefaciens* is a typical phytopathogen harboring CTK biosynthetic gene *IPT* responsible for its gall-initiating capability on host plants. Morphologically, a nodule is similar to a gall, both being provoked by excessive productions of CTKs and/or the imbalance (or inappropriate ratios) of CTKs and auxins. However, the former is generant as a result of plant root−rhizobium symbiotic interaction and the latter is generant as a neoplasm derived from the pathogen infection site of aerial parts. Moreover, the gall induction by pathogenic *A. tumefaciens* (a close relative of nodulating rhizobia) is dependent on CTK biosynthetic genes such as *TZS* and *IPT* that encode, respectively, the enzymes functioning adaptatively in prokaryotic (bacterial) and eukaryotic (plant) cells.[286] The presence of such enzymes in pathogens could help the follow-up investigations concerning the evolution of the root nodule symbiosis or vice versa as well as how and why some bacteria ride the fence of the pathogen−symbiont boundary.[287]

Concerning the starting material for the biosynthesis, CTKs and their biosynthetic precursors were found in the culture supernatants of several endophytes, such as endophytic fungus *Rhodotorula minuta* of Scots pine buds, bacteria *Pantoea agglomerans* of barley seeds, and *Methylobacterium extorquens* of the same pine sprout.[288,289] Moreover, zeatin, a predominant member of CTKs, was reported to be produced by many other microbial species including the bacteria *Agrobacterium rhizogenes,*[290] *A. tumefasciens*,[290] *Paenibacillus polymyxa*,[291] *Pseudomonas fluorescens*,[292] *P. syringae*,[290] and *P. solanacearum*,[290] as well as the fungi *Funalia trogii*[293] and *Trametes versicolor*.[293] In addition to these, some cyanobacteria such as *Synechosystis*, *Oscillatoria*, *Phomidium*, *Chroocidiopsis*, and *Anabaena* species have recently been identified as new CTK producers. Furthermore, *in planta* secretions of CTK by the cyanobacteria might confer the localized resistance of *Arabidopsis thaliana* against *Pseudomonas syringae pv tomato* DC3000, and of tobacco aganist *Pseudomonas syringae tabaci*.[294]

As a conclusive presumption, CTKs function across the *planta* and microbial world, in addition to their actions toward mammalian cells (discussed in section 5.1), which would pave a path for the discovery of new therapeutic agents required urgently for treating human cancers.

6. GIBBERELLIN

As a major set of plant hormones, gibberellins (GAs) play significant roles in regulating plant growth and development, ranging from seed germination and vegetative growth to flowering and flower development.[75] Recognized as a big group of diterpenoids, GAs are derived biosynthetically from geranylgeranyl diphosphate in plants.[295] In spite of a wealth of publications focusing on the function, structure, biosynthesis, and deficient mutants of GAs in plants, few reports could be consulted with regard to their possible roles in mammalian cells until two GA3 analogues A and B, transformed chemically from GA3, were characterized as potent antitumor agents (Figure 10).[77] Furthermore, a recent U.S. patent has revealed that compounds like GAs and their derivatives can be used for the preparation of a pharmaceutical composition for treating diabetes and its complications including obesity, micro- and macrovascular diseases, nephropathy, neuropathy, eye disorder, and diabetic ulcerations.

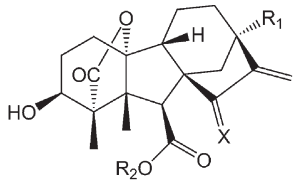

Figure 10. Structures of gibberellin GA3 and its antitumor analogues A and B.

The medicaments result in the normalization of serum glucose level and physiological performance associated with diabetic patients.[78] These observations suggested that the skeleton shared by GAs should be of significance in the action of thus-constructed compounds toward nonplant cells/organisms.

7. BRASSINOSTEROIDS (BRS)

In the late 1970s, brassinolide was identified as the first BR member from bee-collected rape pollen.[296] Following the detection of brassinolide in all plant species examined to date,[297−299] BRs collectively refer to plant-generated steroidal hormones that stimulate plant growth at nano- or micromolar concentrations with brassinolide and castasterone accepted as the two representative BRs possessing ε-lactone and cyclohexanone moieties, respectively (Figure 11). Moreover, BRs have been demonstrated to occur in almost every part of plants including pollen, floral buds, fruits/seeds, vascular cambium, leaves, shoots, and roots.[300] Using sterols as precursors, BRs can be biosynthesized in vivo, sharing structural similarity to the mammalian steroid and insect ecdysteroid hormones in the tetracyclic nucleus coupled with multiple oxidations.

BRs play key roles in regulating a variety of plant physiological processes such as growth, differentiation, cell elongation, disease resistance, stress tolerance, and senescence, with brassinolide being the most potent one.[80] They have been demonstrated to exert stimulatory effects on cell division in numerous plant species and cell culture lines,[301−303] and further disclosed to stimulate cell division during the early phase of cell cultures, indicative of their possible roles as rate-limiting factors in cell cycle induction.[304] Moreover, BRs can function in place of CTKs since both BRs and CTKs are able to induce *cycD3* gene expression.[305] In particular, the 24-epimer of brassinolide, named 24-epibrassinolide (Figure 11), has been extensively investigated due to its wide-spectrum practical applications in agrochemicals and available evaluation of potential agricultural utility of a variety of formulations.[306]

7.1. Antitumor Activity

Given that the cellular and molecular mechanisms concerning how BRs act on mammalian cells are almost unknown, the cytotoxic assays for the effect on mammalian cancerous cell lines represent a good starting point of the topic. Without affecting normal cells, the natural BRs 28-homocastasterone and 24-epibrassinolide (Figure 11) were demonstrated to inhibit at micromolar concentrations in a dose-dependent mode the growth of human breast (MCF-7 and MDA-MB-468) and prostate cancer cell lines (LNCaP and DU-145). The two BRs could cause the cell cycle arrest in G_1 phase for the MCF-7, MDA-MB-468, and LNCaP cells while triggering apoptosis for

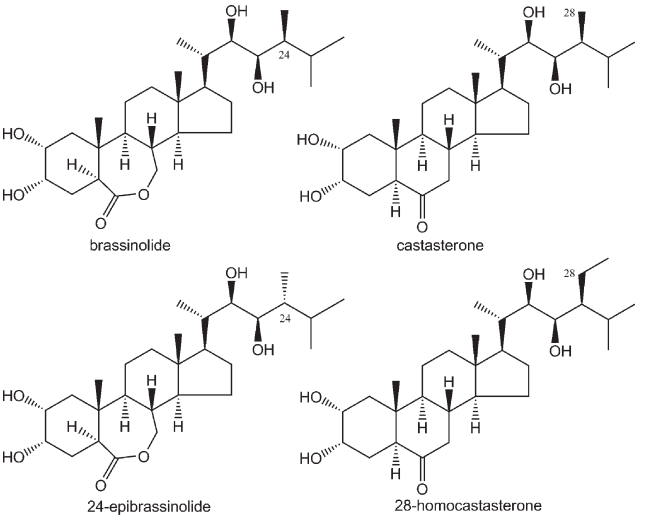

Figure 11. Structures of brassinolide, 24-epibrassinolide, castasterone, and 28-homocastasterone.

the MDA-MB-468 and LNCaP cells.[82] Moreover, the natural brassinolide was shown to be cytotoxic toward androgen-independent human prostate cancer PC-3 cells in a time- and dose-dependent manner. Furthermore, the discerned cancer cell death appeared to be ascribed to apoptosis as evidenced from a combination of flow-cytometric analysis, fluorescence, and transmission electron microscopic approaches, which detected as well the elevated activity of caspase-3 and the downregulation of antiapoptotic protein Bcl-2, two notable indicators for apoptosis induction.[83] The findings suggested that brassinolide, along with its analogues, could be of value in the development of the antitumor drugs.

In addition, both BRs and their synthetic derivatives were recently investigated using the endothelial primary cells including human umbilical vein endothelial cells (HUVEC) and human mammary epithelial cells (HMEC), demonstrating that some of the steroidal compounds could inhibit considerably the proliferation and migration of human endothelial cells to result in apoptosis. In particular, the inhibition of migration is reversely linked to the development of new blood vessels, the formation of new tumor centers, and the growth of cancerous tissues.[84] These results suggest a potential antiangiogenic activity of BRs on endothelial cells, thereby facilitating our understandings about their pleiotropic effects across *planta* and animal kingdoms.

7.2. Antiviral Activity

Some natural BRs and synthetic analogues were disclosed to be antiviral in vitro against several pathogenic viruses such as herpes simplex virus type 1 (HSV-1), arenaviruses, and measles virus.[85,86] HSV-1 is the pathogen eliciting human ocular disease termed herpetic stromal keratitis (HSK), accounting for a leading risk factor of ocular impairment and blindness.[307] Wachsman et al. synthesized and bioassayed an array of analogues of the natural brassinosteroid (22*R*,23*R*,24*S*)-2α,3α,22,23-tetrahydroxy-5α-ergostan-6-one.[85] The substantially potent compounds against HSV-1 were (22*S*,23*S*,24*S*)-2α,3α,22,23-tetrahydroxy-5α-ergostan-6-one, (22*R*,23*R*)-3β-acetoxy-22,23-dihydroxy-5α-cholestan-6-one, (22*S*,23*S*)-3β-bromo-22,23-dihydroxy-5α-cholestan-6-one, and (22*S*,23*S*,24*S*)-3β-bromo-5α,22,23-trihydroxyergostan-6-one (the most active one). Moreover, the bioactive BR derivatives displayed similar selectivity indexes (SI) to that of

foscarnet (trisodium phosphoformate), a drug prescribed clinically for treating HSV-1 infection.[308] In view of the speedy escalation in the in vivo drug-resistant viral mutants, it is intriguing that these derivatives exhibited similar activity against TK^+ and TK^- HSV-1 strains.[309] The antiviral activities of BRs suggested that they could serve as a novel class of antiviral compounds, though further work is desired to elucidate the precise mechanism and the SAR for their antiviral actions toward human pathogenic viruses. Meanwhile, resembling the antistress activities of the natural BRs in plant via the induction of the heat shock protein expression,[310] the synthetic BR analogues were demonstrated to possess as well growth-promoting activities *in planta*[85] by the classical bioassay using rice lamina inclination as an indicator.[311]

7.3. Immunomodulatory Activity

Because BRs belong to 5α-cholestane steroids, their immunomodulatory effects in mammals may follow both from their structural similarity to the mammalian steroid hormones mediating a number of metabolic pathways and from their roles in plants as immunomodulators when applied at the appropriate concentration at certain stages of plant development.[300,312] The synthetic brassinosteroid (22*S*,23*S*,24*S*)-3β-bromo-5α,22,23-trihydroxyergostan-6-one was shown to be antiviral because its administration could reduce the incidence of murine HSK.[87] The action might be attributed to the regulatory effect of the bromated sterol on immune-mediated stromal inflammation in vivo rather than a direct antiviral effect because the percentage of mice with ocular lesions declined substantially 5 days after the exposure termination of the synthetic BR. This assumption was further rationalized by the fact that no substantial differences in the viral titers of murine eye specimens were discerned among treated and untreated mice.[87] Moreover, the synthetic BR could impair the HSV-1-induced activation of NF-κB and attenuate significantly the TNF-α secretion in HSV-1-infected NHC (a human conjunctival cell line), whereas the compound could promote the IL-6 production after HSV-1 infection in both cell types. Moreover, the production of cytokines TNF-α and IL-6 was significantly reduced in a bacterial lipopolysaccharide (LPS)-stimulated macrophage cell line after treatment with the compound. Both TNF-α and NF-κB play important roles in the pathology of HSV-1 infection, and TNF-α generated predominantly by monocytes and macrophages is crucial to the development of the mammalian humoral immune responses, with which NF-κB is also associated.[313] Furthermore, the virus HSV-1 might induce the activation of NF-κB by interacting with toll-like receptor (TLR)-2 to generate an array of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6.[314,315] This virus was found to encompass several consensus-binding sites for NF-κB in the promoters, which was employed to enhance its replication and multiplication.[316] Additionally, HSV-1 was further demonstrated to induce a durable NF-κB translocation to the nuclei of NHC and Vero cells.[317] These observations collectively substantiated that (22*S*,23*S*,24*S*)-3β-bromo-5α,22,23-trihydroxyergostan-6-one could most likely modulate either as an elicitor or as a suppressor of the immunoinflammatory responses independent of the type of test cells.[88]

However, this brominated BR may have other antiviral mechanisms such as inhibition on viral protein synthesis and mature virion formation of vesicular stomatitis virus in Vero cells.[318] Further investigations are needed to decipher the underlying mechanism through which BRs and their analogues such as (22*S*,23*S*,24*S*)-3β-bromo-5α,22,23-trihydroxyergostan-6-one act in the immune responses in vivo so that they can be precisely used for treating HSV-1-related diseases such as ocular disorder. Furthermore, the BR structures are similar in part to those of the vitamin D series such as vitamin D2 (Figure 12), suggesting that they could have more biological actions.

8. STRIGOLACTONES

Strigolactones are sesquiterpenes containing a tricyclic lactone core (A, B, and C rings) in conjuction via an enol ether bond with an α,β-unsaturated furanone moiety (D ring) (Figure 13). They were previously identified both as seed germination stimulants of the weeds *Striga* and *Orobanche*, and as signaling molecules on hyphal branching of some arbuscular mycorrhiza (AM) fungi. Inconsistent with the assumed sesquiterpene origin, the strigolactones were indicated to be biosynthesized by the carotenoid pathway.[319] The strigolactone is predominantly produced in roots from carotenoid and subsequently translocated to shoots, where it inhibits subapical shoot outgrowth. Accordingly, the compound accords with the classical definition of a phytohormone because it is produced in one tissue and translocated to another where it displays a potent effect on plant growth.

In addition to auxins and CTKs, strigolactones have been accepted as the third class of phytohormones regulating the plant shoot branching on the basis of the recognized activities ascertained with the latest advancements in plant molecular, genetic, and analytic techniques.[90−92] In 2008, two independent groups both reported that strigolactones are either themselves phytohormones or the biosynthetic precursors thereof based on their work with shoot branching mutants of pea (*ccd8* mutation) and rice (*d* mutation).[90,91] Supplementation to those mutant plants with small amounts of strigolactones could rescue the mutant phenotype that is highly branched as incurred by impairment in strigolactone synthesis. Accordingly, strigolactone is at least in close appropinquity to phytohormone if not an actual one.

Another investigation was performed concerning the effect of GR24 (a strigolactone analogue, Figure 13) on the AM fungus *Gigaspora rosea*.[93] The GR24 treatment of the fungus resulted in the activation of fungal oxidative metabolism as evidenced from the coelevation in the NADH concentration, the NADH dehydrogenase activity, and the ATP level of the fungal cell. Moreover, the genes associated with mitochondrial metabolism and hyphal growth were upregulated, and the fungal mitotic activity was stimulated.[93] As observed earlier by the same group, strigolactones might act as a potent and rapid stimulant of cell proliferation in the AM fungus *G. rosea* at a concentration as low as 10^{-13} mol/L.[320] Furthermore, strigolactones displayed stimulatory effects on the spore germination of a set of phylogenetically distant AM fungi such as *G. rosea*, *Glomus intraradices*, and *Gl. Claroideum*, with the mechanism suggested to be associated with a rapid increase in mitochondrial density and respiration.[320] Kinetically, strigolactones were shown to trigger expression of fungal genes related to mitochondrial activity (1 h posttreatment), followed by increases in the respiration rate (1.5 h posttreatment) and mitochondrial reorganization (4 h posttreatment), and finally fungal ramification stimulation (24 h posttreatment), highlighting that the branching response is the outcome of a metabolic switch in fungi.[321] There are also clear indications that strigolactones are involved in the signaling cascade at the presymbiotic stage (e.g., hyphal branching before fungal contact with the plant roots), and that the strigolactone

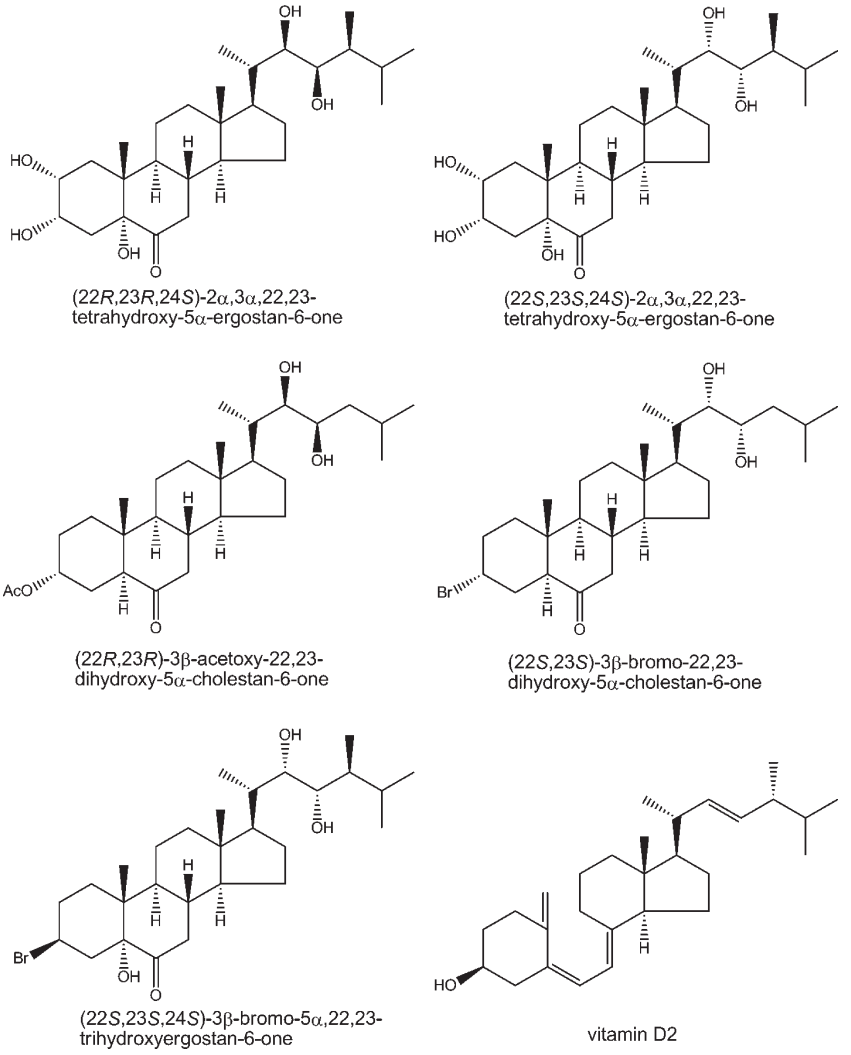

Figure 12. Structures of bioactive BR analogues and vitamin D2.

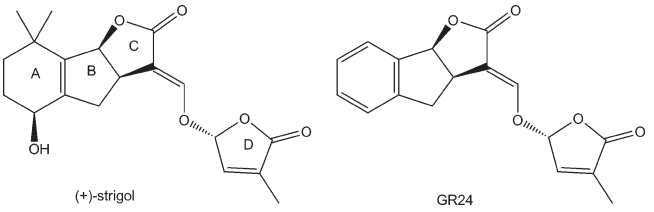

Figure 13. Structure of strigolactones (+)-strigol and GR24.

levels are decreased in root exudates once plants are mycorrhizal, indicating their implication at later stages after symbiosis establishment.[322] However, further investigations are necessary to elucidate their precise functions during each stage of the AM symbiosis.

The occurrence of endocellular bacteria is a well-recognized phenomenon with AM fungi, thus constituting the triple symbiotic system (plant−fungus−endocellular bacterium).[94] Interestingly, the exposure of fungal spores to strigolactones resulted in an increased expression of *ftsZ* gene (a marker gene for bacterial division), which encodes a major bacterial cytoskeletal protein, a homologue to the eukaryotic tubulin.[95] Tubulin is a kind of highly conserved protein localized in the centrosome of eukaryotes ranging from yeast to mammals and is associated with the assembly of microtubules during the cell cycle. Thus, the commonness may exist in modulatory mechanisms for fungal cell mitosis/bacterial cell division. These ascertained activities of strigolactones highlighted the possibility that this family of phytohormones would exert certain actions toward mammalian cells, for instance, targeting cytoplasmic or subcellular (i.e., mitochondrial) receptors associated with lipid catabolism, respiration, and mitochondrial biogenesis, as do thyroid hormones.[323]

Given that fungi are lower members of eukaryotes, which, along with animals and plants, constitute the living organisms characteristic of a cell nucleus within the plasma membrane, it may be reasonable to anticipate that strigolactones may serve as modulators in mammalian cells for cellular mitosis, mitochondrial biogenesis, and respiration metabolism. Although their action toward mammalian cells awaits investigation, strigolactones could affect the AM fungal branching, suggestive of their cross-kingdom actions at least across the *planta* and microbial communities.

9. ABSCISIC ACID

Abscisic acid (ABA) is a ubiquitous phytohormone that regulates seed germination, development, and response to the

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abiotic stress adaptation.[96,97] As a plant signal molecule, ABA is perceived and recognized at both the intra- and extracellular levels, notably mediating important functions in response to abiotic stresses including salt, cold, drought, and wounding. Compounding the recent investigations about the ABA-dependent signaling and transport processes, particularly the identification of an ABA transporter, the engineering of drought-tolerant plants becomes a promising means for agronomically significant plants that can be supposed to survive or thrive in the stressful environment.[324] In addition to helping plants adapt to the abiotic challenges, ABA has recently been found to improve the growth and development of some fungi,[54] as well as to be protective for the survival of some animals such as marine sponges,[98,99] hydroids,[100] and mammals.[101,102] The similarity between these findings is mainly associated with the ABA-mediated stress response because ABA seems to regulate both defense responses in plants and immune functions in animals. Further investigations are desired for recognizing its targets in nonplant organisms, as well as for understanding the mechanisms concerning how it modulates immune-associated processes in animals.

ABA has recently been accepted as an endogenous pro-inflammatory cytokine in human granulocytes because it activates granulocyte defensive functions including phagocytosis, migration, productions of ROS and nitric oxide, chemotaxis, and chemokinesis. These actions were primarily realized through a receptor-mediated signaling pathway involving a membrane PTX (pertussis toxin)-sensitive G-protein/receptor complex, cAMP overproduction, PKA (protein kinase A)-dependent phosphorylation of the human ADP-ribosyl cyclase CD38, and subsequent generation of cADPR (cADP-ribose) that leads to the elevation of intracellular Ca^{2+} levels.[101,325] This mammalian signaling pathway is similar to that mediated by ABA in plants.[326] Moreover, this phytohormone stimulates the insulin secretion of human and murine pancreatic β-cells and of rat insulinoma cell lines at nanomolar concentration through a signaling pathway orthologous to that in human granulocytes.[327] The autocrine production of ABA from glucose-stimulated human and rodent insulin-releasing cells, along with the release of ABA by activated inflammatory cells granulocytes[101] and monocytes,[102] suggests that ABA possibly contributes to the network of cytokine signaling exchange and cross-talk between inflammatory and pancreatic β-cells, both playing fundamental roles in the development of the metabolic syndromes and type II diabetes.[103,104]

By probing human gene and protein interaction networks, a total of four protein homologues of *Arabidopsis* ABA-related genes including NCOA6 (nuclear receptor coactivator 6, also called PPAR-interacting protein), DNTTIP2 (deoxynucleotidyltransferase terminal-interacting protein 2), MAPK1/2 or ERK1/2 (mitogen-activated protein kinase 1), and EDF-1 (endothelial differentiation factor) was identified to anchor in the PPARγ (peroxisome proliferator-activated receptor γ) network in mammals. The transcriptional activity of PPARγ and other nuclear receptors is modulated both by ligand binding and by the recruitment of nuclear receptor coactivators including NCOA6 that bridges CBP/p300 (cAMP response element-binding protein) and PBP (PPARγ-binding protein), implying that ABA may regulate PPARγ activity indirectly by interacting with its coreceptors.[105,328,329]

Given the pivotal roles of PPARγ in a variety of mammalian anti-inflammatory and metabolic processes, the observations that ABA upregulates PPARγ expression in vivo, along with the in vitro elevation of PPARγ activity by ABA, may shed light on the development of new strategy for the prevention and treatment of chronic inflammation and autoimmunity diseases. Furthermore, ABA has also been shown to be antidiabetic based on the finding that supplementation of ABA into high-fat diets could prevent the onset of type II diabetes in obese db/db (leptin receptor-deficient) mice.[330] Consequently, a possible linkage between ABA-mediated signaling pathway and PPARγ-dependent mechanisms in mammalian cells may contribute to the antidiabetic action of ABA without distinct side effects such as excessive weight gain and fluid retention. The antidiabetic action of ABA in mammals could be further rationalized by the aforementioned prevention of ABA in the development and progression of type II diabetes and associated metabolic syndromes thereof.[103,104]

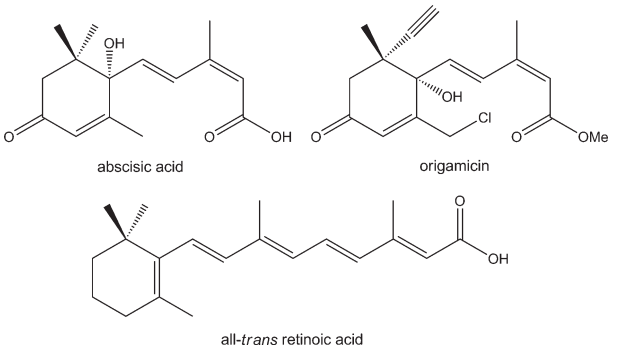

Figure 14. Structures of abscisic acid, origamicin, and all-*trans*-retinoic acid.

Besides its promising actions in antiinflammation and antidiabetic aspects, ABA may also represent a potential cancer treatment because of its ability to control calcium signaling. Its cancer-preventive action might be deduced from a patent issued earlier to Livingston-Wheeler for its application as an anticancer compound,[331] as well as from the recent findings that some of ABA-activated pathways are mechanistically similar to those modulated by chemotherapeutic agents that are in current clinical use for cancer treatment, including anticancer drugs staurosporine, doxorubicin, tamoxifen, and etoposide, all killing the cancer cells by elevating the intracellular Ca^{2+}.[105] Accordingly, ABA may be of great potential as a starting molecule for the development of new therapeutics treating chronic diseases including inflammation, autoimmunity disorders, diabetes, and cancers.

As illustrated in Figure 14, ABA is structurally comparable to all-*trans*-retinoic acid, which has long been a hot topic of biomedicine. So far, all-*trans*-retinoic acid has been proven to have therapeutic properties against an array of human refractory diseases such as leukemia[332] and Alzheimer's disease.[333] However, only a few ABA molecular targets like calcium signaling and G protein-coupled receptors have been identified in vitro in both plant and animal systems. As a newly recognized endogenous pro-inflammatory hormone in human granulocytes, ABA was indicated to stimulate several functional activities of the murine microglial cell line through the second messenger cADPR and an increase of intracellular calcium, potentially representing a new target for anti-inflammatory therapies for treating microglia-induced tissue damage in the central nervous system.[101,334] Recently, ABA was found to be a new signal molecule involved in the development of atherosclerosis, suggesting its important roles in the antiatherosclerotic therapy.[102]

In addition to its actions in plants and animals, ABA and its analogues were found to affect some microbes. As an application

for ABA-based molecular scaffolds for mammalian cellular targets, a group of 18 different ABA analogues was tested for inhibiting HCV replication using a cell-based screen involving subgenomic HCV replicons, showing that origamicin (Figure 14) gave pronounced antiviral activity through inhibiting folding-relevant host proteins.[335] Recently, the endogenous ABA level was indicated to regulate nodulation and nitrogen fixation through decreasing the production of nitric oxide in nodules.[336,337] Furthermore, ABA was demonstrated to contribute to the susceptibility of tomato to the AM fungus.[106] In addition, ABA production controls calcium signaling within the apicomplexan parasite *Toxoplasma gondii*, an opportunistic human pathogen, highlighting its potential therapeutic significance in toxoplasmosis prevention.[338] These data collectively reveal that ABA and its analogues may possess cross-kingdom actions that are of potential value in the field of biomedicine.

10. ETHYLENE

Ethylene, widely recognized as the phytohormone associated with plant growth and development processes such as fruit ripening, became a focused topic of biochemical and genetic research in plant sciences several decades ago.[108,109] In addition to its actions *in planta*, ethylene was found to regulate plant−microbe interactions with its role in the recruitment of culturable endophytic bacteria from native soils.[110] This is very important since some endophytes, while benefiting host plant growth,[339] may gradually become a source of functional biomolecules, presumably as a result of the gene flow during endophytism or interadaptation between recruited microbes and host plants.[340,341] In response to abiotic and biotic stresses including attacks from insects and pathogenic microbes, ethylene normally functions in plants jointly with other stress-related phytohormones such as SA and JA,[342] while sometimes playing decisive roles including modulating cross-talks between SA and JA signaling pathways.[343] Accordingly, it can be presumed that ethylene acts toward nonplant species mainly in an indirect manner.

11. CONCLUDING REMARKS

Owing to their sessile lifestyle in a complex environment, plants have to rely on phytohormones and the combination thereof to regulate the growth and development and to cope with biotic and abiotic stresses including drought, frigidity, high irradiation, animal predation, and attacks from microbes and insects. Similar to animal hormones, classical plant hormones are small-molecule organic chemicals that can regulate at very low concentrations physiological and developmental processes as well as stress adaptations or responses. While plants utilize some phytohormones to endure the inevitable stresses, some pathogenic microorganisms can affect the homeostasis or alter the balance of related phytohormones to antagonize the host immune responses so that they can maximize and speed up their invasion or colonization.[344] This is because two or more interdependent phytohormone pathways may work synergistically or antagonistically through coordinated regulations of common target genes,[345] as exemplified by the recent observation that the BR signaling pathways are actually modulated by ABA[346] and GA.[347] On the whole, the accumulated molecular and genetic understandings on the topic highlight that the plant hormones are cross-linked by emerging upstream and/or more common connections that are not restricted in the plant kingdom.[345] This could explain why some phytohormones are also active in regulating the physiological processes of nonplant organisms.

As a matter of fact, the actions of phytohormones toward mammalian cells have been well substantiated by the recognitions of plant hormones and their analogues as antitumor, antioxidant, and immunoregulatory and enzyme modulatory agents. The scaffolds or pharmacophores including their smart combinations/integrations have been and continue to be important to the relevant drug discovery as if aspirin and indomethin were thoroughly investigated and eventually proven for the long-time clinic prescription. The health-improving effect of phytohormones, together with that of other copresent phytochemicals, may be of referential value in explaining at least in part why a randomly selected vegetarian has normal bone mineral density and body composition,[348] and why the lifestyle pattern that includes a very low meat intake is associated with greater longevity.[349] The action of phytohormones toward microorganisms is another important concern since some plant hormones and their analogues showed pronounced antibacterial, antifungal, and antiviral activity. This is not only consistent with their phytoprotective roles in helping plants adapt stresses raised by numerous microbial pathogens but also valuable in searching for new antimicrobial agents, necessitated urgently owing to the drug resistance discerned with most of the existing antibiotics. Interestingly, some plant hormones benefit the growth of specific communities of microbes as exemplified by strigolactones that serve as branching factors for some AM fungi in association with plant roots where *Striga* species parasitize.[13] Plants, as the starting organisms of the food chain, are able to produce phytohormones. Some phytohormones and the related intermediates could be absorbed and used by the herbivore as the defensive arsenal preserved for postoviposition survivals. This is well illustrated by the observation that JA, SA, and one of its metabolic precursors, benzoic acid (also a well-known antiseptic agent), were codetected in eggs of the fruit-feeding fly *Rhagoletis pomonella*.[350]

The cross-kingdom actions of phytohormones discussed in this review may reflect a common cellular machinery possibly acquired by both plants and mammals during the long-time coevolution to survive and to grow well in the unfavorable environmental conditions. At molecular level, numerous genes and the associated proteins have undergone divergent evolution, with some genes being extinct, some being silenced, and some experiencing loss-of-function. Interestingly, a set of important events including a lasting increase in cytoplasmic calcium, the release of ROS, the generation of nitric oxide (NO), the activation of MAPKs, and final cellular events such as cytoplasmic shrinkage, chromatin condensation, and DNA breakdown occur both in the plant defenses against pathogen assaults and in mammalian immune responses to pathogen/carcinogen challenges. Accordingly, further in-depth understandings about the privileged scaffolds and exact mechanisms of phytohormones in mammals and plants may be of wide interest and may facilitate the elucidation of the inherence ubiquitous in living organisms. In addition, a couple of more fundamental questions awaits the follow-up endeavor. Concerning the generation, more data are desired to clarify whether the phytohormones are produced independently by plants or by a plant−microbe interaction process, or merely by some plant-associated microbes, since some plant hormones such as IAA producible by many fungi and bacteria are also emerging as a microbial metabolic and signaling molecule.[241] Regarding the verification of new phytohormone

members, more attention should be paid timely and sophisticatedly to "phytohormone candidate" natural products, if learned from the fact that strigolactone had been "unnoticed" for about three decades before being recognized as a new plant hormone.[351] As to the plant−microbe interaction, the precise role of phytohormones in the plant resistance and susceptibility to pathogens deserves more attention because the plant innate immunity involves perception of PAMPs,[352] which is analogous to Toll-like receptors in mammals.[353] It is believed that the renewed understanding on the topic may offer fresh opportunities for an increased crop production and/or effective controls of refractory diseases such as cancers and the infections incurred by emerged and emerging drug-resistant pathogens.

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BIOGRAPHIES

Lan Lin, born in Wuhan, received her B.Sc. in Microbiology (1991) at Wuhan University, P. R. China. After working for an institution of biological products, she returned to university for graduate studies and participated in the research on antitumor phytochemical taxol. She got her M.Sc. in Biology (2004) from McMaster University, Hamilton, Canada, and her Ph.D. in Biology (2010) from Nanjing University, where she investigated the mechanism of plant−microbe (endophyte) interaction mediated by phytohormones, under the guidance of Prof. R. X. Tan. She is currently working as a faculty member in the Dept. of Bioengineering at Southeast University, P. R. China.

Ren Xiang Tan, born in Jiangsu (1960), received his B.S. in Pharmacy in 1983 and his M.S. in Medicinal Chemistry in 1986 from the China Pharmaceutical University, and his Ph.D. in Organic Chemistry in 1990 from Lanzhou University, where he spent his two-year postdoctoral research period. After his joining Nanjing University as associate professor in 1992, he was promoted as Professor of Botany (1994), Chair Professor (1999). He has been successively visiting scholars to the Institute of Organic Chemistry, Technical University of Berlin, Berlin, Germany (Prof. F. Bohlmann); Institute of Pharmacognosy and Phytochemistry, University of Lausanne, Lausanne, Switzerland (Prof. K. Hostettmann); and the Institution of Oceanography, University of California, San Diego, CA, U.S.A. (Prof. W. Fenical). His work interest has focused on the structure and function of biomolecules and plant−microbe interactions. Besides serving as editor-in-chief of 4 monographs, he has authored 218 scientific publications.

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ABBREVIATIONS

ABA	abscisic acid
AKR	aldo-keto reductase
AM	arbuscular mycorrhiza
AML	acute myelogenous leukemia
APL	acute promyelocytic leukemia
ATP	adenosine triphosphate
BAK1	BRI1-associated receptor kinase 1
BRI1	brassinosteroid-insensitive 1
CAT	catalase
Caspase	cysteine aspartyl-specific protease
CBM	*N*-(4-chlorobenzoyl)-melatonin
CJ	*cis*-jasmone
COX	cyclooxygenase
CTK	cytokinin
ERK 1/2	extracellular signal-regulated kinase1/2
Fas	factor associated suicide
GA	gibberellin
GDEPT	gene directed enzyme prodrug therapy
GPx	glutathione peroxidase
GR	glutathione reductase
GSH	reduced glutathione
GUS	β-glucuronidase
HCV	hepatitis C virus
HRP	horseradish peroxidase
HSDs	hydroxysteroid dehydrogenases
HSK	herpetic stromal keratitis
HSP 72	heat shock protein 72
HSV-1	herpes simplex virus type 1
5-HT	5-hydroxytryptamine
i^6A	N^6-isopentenyladenosine
IAA	indole-3-acetic acid
IAM	indole-3-acetamide
IκB	inhibitor of NF-κB
IKK	IκB kinase
IPT	isopentenyl transferase

IPyA	indole-3-pyruvate
IL	interleukin
JA	jasmonic acid
JNK	Jun N-terminal kinase
KR	kinetin riboside
MAPK	mitogen activated protein kinase
MEK1/2	MAPK/ERK1/2
MJ	methyl jasmonate
mPDF	mitochondrial PDF
MSO	mitochondrial superoxide
NBT	nitroblue tetrazolium
NF-κB	nuclear factor-κB
NIN	nodule inception
Nod	nodulation
NSAIDs	nonsteroidal anti-inflammatory drugs
PAH	polyaromatic hydrocarbon
PAMPs	pathogen-associated molecular patterns
PCD	programmed cell death
PDF	peptide deformylase
PG	prostaglandin
PGD_2	prostaglandin D_2
PGE_2	prostaglandin E_2
$PGF_{2\alpha}$	prostaglandin $F_{2\alpha}$
PGH_2	prostaglandin H_2
PGHS	prostaglandin H synthase, also called COX
PGI_2	prostaglandin I_2
$15dPGJ_2$	15-deoxy-$\Delta^{12,14}$ PGJ_2
P-gp	P-glycoprotein
PPARγ	peroxisome-proliferator-activated receptor-γ
PrP	prion protein
RNP	ribonucleoprotein
ROS	reactive oxygen species
SA	salicylic acid
SAR	structure−activity relationship
SOD	superoxide dismutase
TGF-β	transforming growth factor-β
TNF-α	tumor necrosis factor-α
TRIT1	tRNA-IPT-1
tRNA	tRNA
Trp	tryptophan

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