Chemistry Research Journal, **2022, 7(6):45-51**
Available online www.chemrj.org

Review Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

Development of Herbal and Microbial Natural Products for Use in Biomedicine and Agriculture

Amber S. Gad

Chemistry of Natural and Microbial Products Department, National Research Centre, Giza

Abstract Plants as a host for co-existing endophytes represent living chemical factories for safe natural products of biomedical significance, however these products may cause adverse effects on interaction with other supplements. The aim of this review was to investigate some value-added metabolites of pharmaceutical, cultural concerns and recreational drugs especially for cancer and infectious diseases. The advanced analytical utensils, genome engineering systems, and microbial culturing approaches resulted in discovery of new natural products.

Key words: Endophytes, ecology, phytomedicine, alkaloids, genetic coding, abiotic stress

Introduction

Among the important factors in animal breeding are the microorganisms that live within the plants and animals [1]. The effects exerted on animals by dietary plants are due to the plant's secondary metabolites or commensal microorganisms, which arises from seeds [2]. The production of secondary metabolites (SM) is estimated in algae, fungi, microbes, herbal plants, and in invertebrate animals. [3,4]. Considering a plant potential toxicity depend on the metabolic status of the animal, the interaction with other secondary metabolites, and the quantity received through the animal diet. Also, these secondary metabolites differ with changes in premature leaf senescence, plant bolting, the growth seasons, heat and the day length. Their biosynthesis and accumulation show organ or tissue specificity [5]. SM are low-molecular-mass which formation is generally inhibited during logarithmic growth then weaken during the suboptimal or stationary growth phases [6]. SM balance health promoting processes regarding the excretion of toxic products to encourage the functional status of the cells [7].

Phytochemicals natural functions

While ethnomedicinal methods declined in countryside population [8], many of SM are part of the Materia medica, e. g., alkaloids, cardiac glycosides ...etc. when acting as sexual hormones, differentiation effectors or aid in biological properties including anti-angiogenesis. Nicotine, and rotenone are used as antimicrobial agents (pentacyclic terpene, arjunolic acid), antifungal, anti-inflammatory, antimalaria, anti-parasitic, antioxidant, anti-tumor, antiviral, or anticancer (Taxol) compounds [9]. Briefly, SM play a role in symbiosis interaction with signals for communication between plants and symbiotic structure, may be used in agriculture as natural protectants against biotic pressure (bacteria, fungi, nematodes, insects, or herbivorous deterrents) [10]. They help in attraction of pollinator and have a role in metal transportation, stimulator, (such as caffeine, nicotine, ephedrine) antihelminth, herbicides, insecticide pyrethrin and phytotoxic and tolerant against pest and diseases (iso flavonoids and phenylpropanoid derivatives) [11] .Similarly , penicillin, and vancomycin antibiotics with other metabolite have bulk market potential. Medicinal essential oils are important for flower and fruits aromas, and color. Also, essential oils, capsaicin, piperine, etc. act as flavor used in foodstuffs and beverages. SM help as precursors for the synthesis of plastics, natural dyes, and poisons (strychnine). Some were reported as hallucinogens [morphine, heroin, cocaine, tetrahydro cannabinol etc.] and cholesterol lowering (lovastatin) properties, that are used as fine chemicals in drug development [12-15].

Phytochemicals in horticultural crops

Livestock toxicosis could then be avoided without losing the benefits of the symbiosis by applying endophyte-grass combinations that are safe for livestock but that promote yield and resistance to pests and pathogens.

Microorganisms that live in the plants which are renewable SM resources are significant factors in preservation of agricultural animals. The protective nature of the endophytes is due to anti-insect and antimammalian alkaloids presence. Four alkaloid classes have been associated with the fungal endophytes: the ergot alkaloids (lysergic acid and ergovaline), the indole- diterpenes (paxilline and lolitrem B), a pyrrolopyrazine (peramine), and the saturated amino-pyrrolizidines (loline, norloline, N-acetylloline, and N- formylloline, etc..., collectively called lolines). Three of the four alkaloid classes have been produced by endophytes grown in culture [16]. The most potent against insects are peramine and lolines whereas those most potent against grazing mammals are indole-diterpenes and ergot alkaloids. [1] examine a spectrum of agriculturally important plant and co-exist-fungal products including essential oils, alkaloids, isoflavones and nitrates.

Factors regulating herbal natural products

SM vary within the plant species, developmental stage, genetic and other agroclimatic factors especially light. Irradiation photoperiod, wavelengths ,and light quality affect stomatal density, the stoma size, the number of chloroplast per a cell, the chloroplast size, the dark respiration rate, the light saturation point, the light compensation point, the leaf size, specific leaf area, above ground dry mass, the number of grana per chloroplast, the number of lamella per granum, the thickness of the grana, the apparent quantum efficiency, the chlorophyll content, and consequently secondary product synthesis [17], e.g. accumulation ,yield and content of alkaloids , hexa-decanoic acid, flavonoids, phenolic acids and spermine are affected by light quality .UV stress , pathogen infection, temperature, drought flooding , salinity, and soil nutrients , [18-21]. Recently, artificial light sources have been used in controlled environments for the production and preservation of medicinal germplasm [22-24]. i.e., biochemical secondary metabolic process in medicinal plants depend on CO_2, ozone, heavy metals, and minerals [18,25]. However, a change in one factor may convert the content of SMs even if other factors remain constant [20]. All above conditions serve quality control and improvement of clinical healing effects by altering plant genomes or growth conditions [5].

Phyto microbiome activity

Secondary metabolites have survival functions as multi stress tolerance [26-27], take part in the mechanism of frost tolerance, nutrient storage, structural reinforcement, photo protective, and UV-Vis's absorption [28].

Flavonoids, In the mangosteen plant e.g., are generally in the form of tannins and xanthones, which are contained in higher plants that are used as food sources, are found to possess strong antioxidants, anti-inflammatory, and antimicrobial properties.

Researchers highlighted SM abundance (e.g., coumarins, benzoxazinoids, camalexin, and triterpenes) responsible for shaping the composition and function of the plant microbiome e.g., microbiome composition, nutrient mobilization, pathogen suppression, and hormonal signaling [27]. Similarly, plant microbiomes share in these processes directly or indirectly by regulating plant metabolism. Studies proved that plants can influence their microbiome by secreting various metabolites and microbiome influence the metabolome of the host plant [29,30]. A recent review stated that endophytic fungi help crop plants in better absorption of soil nutrients, increase soil fertility, produce growth promoting substances, and secrete metabolites that act as bio-pesticides.

Some plants, such as Withania and Artemisia, possess medicinally important phytoconstituents like withanolides, withaferin, withanone, asiaticoside, madecassoside, and artemisinin essential oil, etc. These compounds have magnificent importance as drugs [15,31,32]. Artemisinin, arteannuin-B, sesquiterpenoid artemisinic acid, dihydroartemisinic acid content were positively controlled by the plant growth and development, however negatively regulated by water loss stress. Interestingly, some of minor monoterpenes, all sesquiterpenes and other low molecular weight volatiles essential oil components were induced by water deficit factor. Camphor which is the major essential oil constituents did not alter much while 1, 8 cineole was regulated during development of plant and water stress conditions. Water deficit stress causes a decrease in glandular trichome density and size as well [33]. The microbes from various habitats including plant microbiomes (epiphytic, endophytic rhizosphere) and extreme microbiomes (psychrophilic, thermophilic, acidophilic, alkaliphilic, xerophilic, and halophilic) produce secondary metabolites of different uses.

Natural products from bacteria and actinomycetes for drug discovery

While some enzymes, as primary metabolites are regulated by CCR (carbon catabolite repression) mechanism in bacteria and fungi [34] SM production arises from intracellular intermediates (amino acids, sugars, fatty acids, etc.), which are condensed into more complex structures by defined biochemical pathways but usually formed during the late growth phase and possess no obvious function in cell growth, and their biosynthesis is regulated after cells stopped dividing [35,36]. SM are involved in maintaining equilibrium of the organism [7]. There are more than 22,000 known microbial secondary metabolites, 70% of which are produced by actinomycetes, 20% from fungi, 7% from Bacillus spp. and 12% by other bacteria. The *Bacillus subtilis* group produce a range of useful secondary metabolites as animal feed enhancers and antifungal biocontrol agents [37].

Strains of *B. subtilis and B. licheniformis* excrete important non-ribosomal peptides and polyketides metabolites. Metal ions are known to play a critical role in the regulation and blocking of the pathways [22,38].

Actinomycetes as largest bacterial genera that are able to adapt to any environment (Extremophilic, and hydrothermal vents). Among them streptomyces group are considered economically important because more than 10,000 known antibiotics, 50-55% are produced by this genus [39]. Streptomyces griseus and Bacillus subtilis each can produce more than 50 different secondary metabolites [11, 40-42]. Two new caprolactones, ®-10-methyl-6-undecanolide and [6R,10S]-10-methyl-6-dodecanolide were identified in the lipid extract of a marine streptomyces. These caprolactones show a promising activity against cancer cells with low cytotoxicity [43-44].

Microbes as bio medicinal mini-factories

Number of bioactive secondary metabolites molecules are discovered from several marine or halophilic filamentous fungi, algae, or sponges, tunicates, corals, and snails but only a few of them are in clinical trials [40,45]. Nearly half of the metabolite's molecules reside within Penicillium and Aspergillus. The role of secondary metabolites (SMs) as effectors in multidimensional interactions, and how their biosynthesis in symbiosis through complex gene expression regulation mechanisms in the symbiotic structure are through the resemblance or alteration of phytochemical production in host plants [29].

Different chemical structure of secondary metabolites

According to their biosynthetic pathways, plant SMs are categorized into antimicrobial phenolics, terpenoids, hormonal as steroids, polyketides alkaloids, and Flavonoid compounds [46, 47]. Other group of secondary metabolites are, lipids, proteins, isoprenoids, glycosides and shikimates, The most important anti-infective secondary metabolites are *p*-lactams and other antibiotics such as aminoglycosides, tetracyclines, macrolides, lipopeptides, polyenes [36]. Some secondary metabolites used to combat cancer include the anthracycline doxorubicin and bleomycin [47], or used as cytotoxic [48], enzyme inhibitory, neurogenerative [49], nitric oxide inhibitors and suppressors of LPS-induced inflammation [5,50, 51].

SM identification and extract characterization

Extraction after the economic production of microbial compounds, immobilization or fermentation processes will provide a balance with industrial manufacturing regarding (pigments, alkaloids, toxins, antibiotics, gibberellins, carotenoids, etc.). Tissue, organ, and cell culture approach are used in plant -derived SM. Among the huge group of which are rubber, tannins, and cellulose. Tissue, organ, and cell culture approach are used in plant -derived SM. Among the huge group of which are rubber, tannins, and cellulose The screening of secondary metabolites via phenotypic tests is time consuming and sometimes, lack specificity. Nowadays, biological synthesis of nanoparticles makes use of plants, fungi, and bacteria for the synthesis of nanoparticles [52,53]. Recent phytochemistry laboratories use both routine and computational techniques in SM separation. Secondary Metabolite Unique Regions Finder (SMURF) is an important computational web browser that helps to find secondary metabolite biosynthesis genes and pathways in fungal genomes [52]. It provides the precomputed group for most sequenced fungal genomes. Depending on gene's chromosomal position , the PFAM and TIGRFAM entries of genome interpretation and more confident analysis of protein domains, SMURF identification of the adjacent genes estimate the result [34,52].

Availability to genome data and associated bioinformatical tools provides a powerful means for identifying gene clusters associated with the synthesis of secondary metabolites [54]. Their structures were suggested on the basis of GC-MS experiments and manifested by synthesis. The absolute configuration of the compounds confirmed by comparison of the natural and synthetic stereoisomers using chiral gas chromatography [55].

Among traditional techniques VLC is considered for initial fractionation of raw extracts. The incorporation of computational methods in chromatography has facilitated the separation of compounds from a complex mixture .e.g. Ion-exchange chromatography, counter current chromatography, capillary electrophoresis. Other techniques such as GC- MS, LC-MS, LC-NMR, and LC-NMR-MS. Also have been used for the isolation of compounds as well as their structural characterization from a mixture [55].

CC over sephadex LH20 and automated flash chromatography have successfully been used for purification of compounds from the extracts. However, computational techniques such as HPLC, UPLC, and HPCCC been adjusted for the isolation of compounds from an extract or plant fraction depend on separating compounds of similar polarity and even separation of chiral isomers from a mixture.

References

[1]. Aiken G E, Goetsch A L, Michael D. Flythe (2018). Harm and benefit of plant and .edit: Harm and benefit of plant and fungal secondary metabolites in food animal production. Front. vet. sci. 5:36.

[2]. Selosse MA, Baudoin E, Vandenkoornhuyse P. (2004). Symbiotic microorganisms, a key for ecological success and protection of plants. Com re biol.,327(7):639-48.

[3]. Piasecka A, Jedrzejczak-Rey N, Bednarek P. (2015). Secondary metabolites in plant innate immunity: conserved function of divergent chemicals. New phytol; 206(3): 948-964.

[4]. Olga Mosunova Jorge C Navarro-Munoz Jerome Collemare, (2021). From fundamentals to biotechnological applications, ed (s): O. Zaragoza, A. Casadevall. Encyclopedia of mycology, in Encyclopedia of mycology, 2, Els, 458-476.

[5]. Li Y, Kong D, Fu Y, Sussman MR, Wu H. (2020). The effect of developmental and environmental factors on secondary metabolites in medicinal plants. Plant Physiol Biochem; 148:80-89.

[6]. Malik: V.S. (1980). Microbial secondary metabolism. Tr in biochem sci 5, 3, 68-72.

[7]. Semih Otles, Vasfiye Hazal Ozyurt, (202l). Studies in natural products chemistry 435-457 Chap 11 - Biotransformation in the production of secondary metabolites.

[8]. Jose, M. and B B. Sharma et al (2011). Ethnomedicinal herbs used in oral health and hygiene in coastal Dakshina Kannada. J of oral health and comm dent 5(3): 107-111.

[9]. Nair S., J Abraham J. (2020). Natural products from Actinobacteria for drug Discovery. In: Patra, J., Shukla, A., Das, G. (eds). Advances in pharmaceutical biotechnology, Spr, Sing 333-363.

[10]. Bhattacharya, A. (2019). in Effect of High Temperature on crop productivity and metabolism of macro molecules, Acad Press, Technol & Eng - 628 pp.
[11]. Demain A L, Fang A. (2000). The natural functions of secondary metabolites. Adv Biochem eng biotechnol. 69:1-39.
[12]. Sangwan N.S., A.H.A. Farooqi, F. Shabih and R.S. Sangwan (2001). Regulation of essential oil production in plant. plant gro reg 30, 3-21.
[13]. Sangwan RS, Chaurasia ND, et al (2007a). Phytochemical variability in commercial herbal products and preparations of W. somnifera (Ashwagandha). Curr Sci 86:461.
[14]. Sangwan RS, Chaurasiya ND, Lal P, Misra L, et al (2007b). Withanolide A bio-generation in in vitro shoot cultures of Ashwagandha (Withania somnifera Dunal), a main medicinal plant in Ayurveda. Chem pharm bull 55:1371- 1375.
[15]. Sangwan, N.S., Sabir, F., Mishra, S., et al. (2014) Withanolides from Withania somnifera Dunal. Development of cellular technology and their production. Rec pat on biotechnol, 8, 25-35.
[16]. Zhang, Y, Ting H, Qianliang M, et al. (2012). Alkaloids produced by endophytic fungi: A Review natl prod Comm 7 (7X963-968.
[17]. L. X. Zhang, Q. S. Guo et al (2015). Chloroplast ultrastructure, photosynthesis and accumulation of secondary metabolites in Glechoma longituba in response to irradiance. Photos 53(1).
[18]. Ramakrishna A, Ravishankar GA. (2011). Influence of abiotic stress signals on secondary metabolites in plants. Plant sig behav; 6(11):1720-31.
[19]. LI, Y. Konga D, et al. (2020). The effect of developmental and environmental factors on secondary metabolites in medicinal plants. Plant physiol and biochem, 149, 80-89.
[20]. Yang, L., Wen, K. S., et al. (2018). Response of plant secondary metabolites to environmental factors. Molecules (Basel, Switz), 23(4), 762.
[21]. Zhang S, Zhang L, Zou H, et al. (2021). Effects of light on secondary metabolite Biosynthesis in medicinal plants. Front plant Sci.; 12:781236.
[22]. Singh, S and Robinka K (2019). Chap- 12 "Regulation by metal ions." New and future develop in Microbial biotechnol and bioeng J, 151-164.
[23]. Anjum S., Abbasi B. H., et al. (2017). Effects of photoperiod regimes and ultraviolet -C radiations on biosynthesis of industrially important lignans and neolignans in cell cultures of Linum usitatissimum L. (Flax). J. photochem. photobiol. B 167, 216-227.
[24]. Ikram M, Ali N, Jan G, et al (2020). Endophytic fungal diversity and their interaction with plants for agriculture sustainability under stressful condition. Rec Pat Food Nutr Agric.;11(2):115-123.
[25]. Pant P, Pandey S, Dall'Acqua S. (2021). The Influence of Environmental Conditions on Secondary metabolites in medicinal plants: A Literature Review. Chem biodivers. 202110.3389.2021.781236.
[26]. Yadav B , Jogawat A,et al. (2021).Secondary metabolites in the drought stress tolerance of crop plants: A review gene reports 23, 101040.
[27]. Jacoby RP, Koprivova A, Kopriva S. (2021). Pinpointing secondary metabolites that shape the composition and function of the plant microbiome. J Exp bot.;72(1):57-69.
[28]. Verpoorte R, Contin A, Memelink J (2002). Biotechnology for the production of plant secondary metabolites. Phyto chem Rev 1:13-25.
[29]. Alam B, Li J, Ge Q, Khan MA et al. (2021) Endophytic fungi: From Symbiosis to secondary metabolite communications or vice versa? Front Plant Sci.; 12:791033.

[30]. Pang Z, Chen J, et al (2021). Linking plant secondary metabolites and plant microbiomes: A Review. Front in plant Sci. The plant holobiont II: Impacts of the rhizosphere on plant health.621276.

[31]. Chaurasia, P., Sen, R., Bhaumik, S.R. et al. (2012). Preferential repair of DNA double-strand break at the active gene in vivo. J Biol Chem 287(43) ,6414-22.

[32]. Su, XZ., Miller, L.H. (2015). The discovery of artemisinin and the Nobel prize in physiology or medicine. Sci. China life Sci. 58, 1175-1179.

[33]. Yadav RK, Sangwan RS, et al. (2014). Effect of prolonged water stress on specialized secondary metabolites, peltate glandular trichomes, and pathway gene expression in Artemisia annua L. plant physiol biochem.;74:70-83.

[34]. Barrios-Gonzalez J (2018). Chap- 13 - Secondary Metabolites Production: physiological advantages in solid-state fermentation. Curr Develop in Biotechnol and Bioeng. Curr Adv in solid-state fermentation 257¬283.

[35]. Nigam P. S, Singh, A (2014). In Encyclopedia of food microbiology (2nd Ed), 570-578, Edit. Carl A. Batt, Mary Lou Tortorello. Encyclopedia of food microbiol (2nd Edi), Acad Press.

[36]. Sanchez S., Demain A. L (2011). Enzymes and Bioconversions of Industrial, Pharmaceutical, and Biotechnological Significance. Organic Process Res Org Proc Res & Devel, 15, 224-230.

[37]. Kumar Pi, Poonam Choudhary, Hetal H. Dave, Sonu Kkv (2021). Effective management of Vatala Yonivyapda W.S.R Endometriosis by Ayurveda: A Case Report, J Adv Sci Res, 12 (4): 106 -113.

[38]. Abraham, J., & Chauhan, R. (2017). Chapter 6: Bioprospecting of actinomycetes: Computational drug discovery approach. In A. Datta, M. Fakruddin, H. M. N. Iqbal, & J. Abraham (Eds.), Advances in biotechnology (pp. 1-16).

[39]. Subramani, R., & Aalbersberg, W. (2012). Marine Actinomycetes: An ongoing source of novel bioactive metabolites. Microbiol Res, 167, 571-580.

[40]. Peterson D, Damsky W, King B. (2020). The use of Janus kinase inhibitors in the time of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). J Am Acad Dermatol.;82(6): e223-e226.

[41]. Stewart JE, Kim MS, et al. (2006). Molecular characterization of Fusarium oxysporum and Fusarium commune isolates from a conifer nursery. Phytopath. 96(10)1124-33.

[42]. Beth, J., Andre, W., et al (2009). Actinomycetes scale-up for the production of the antibacterial, Nocathiacin. Biotechnol Prog, 25, 176-188.

[43]. Stritzke K, Schulz S, Laatsch H, et al (2004) Novel caprolactones from a marine streptomycete. J Nat Prod.; 67(3): 395-401.

[44]. Atanasov, A. G., Zotchev, S. B., Dirsch, V. M. (2021). International natural product sciences Taskforce, & Supuran, C. T. Natural products in drug discovery: advances and opportunities. Nature reviews. Drug discovery, 20(3), 200-216.

[45]. Saleem M and Nazir M, (2015). Bioactive natural products from marine-derived fungi: Studies in nat prod chem,45, 297-361.

[46]. Kessler A. and Kalske A (2018). Plant secondary metabolite diversity and species interactions, Ann Rev of Ecol, Evol, and Syst, 49:115-138.

[47]. Kumari, S & Updhaya D. et al. (2021). Microbial secondary metabolite Int.l J of Biol, Pharm. and Allied Sci. 10. 488-496.

[48]. Capon, F., Di Meglio, P. et al. (2007). Sequence variants in the genes for the interleukin-23 receptor (IL23R) and its ligand (IL12B) confer protection against psoriasis. Hum Genet ,122, 201-206.

[49]. Cui CB, Kakeya H, Okada G, Onose R (1995). Tryprostatins A and B, novel mammalian cell cycle inhibitors produced by Aspergillus fumigatus. J anti (Tok). 48(11), 382-4.

[50]. Zhang P., Lu Q. (2018). Genetic and epigenetic influences on the loss of tolerance in autoimmunity. Cell & Mole Immunol; 15(6): 575-585.

[51]. Frisvad JC, Larsen TO. (2015). Chemo diversity in the genus Aspergillus. Appl Microbiol Biotechnol. 99(19) ,859-77.

[52]. Nora Khaldi, F T. Seifuddin, et al (2010). SMURF: Genomic mapping of fungal secondary metabolite clusters. Fungal gen and Biolog. 47(9): 736-741.

[53]. Ankamwar, B., Kirtiwar, S., Shukla, A.C. (2020). Plant-mediated green synthesis of nanoparticles. In: Patra, J., Shukla, A., Das, G. (eds) Advances in pharm biotechnol. Spring, Sing.

[54]. Harwood CR, Mouillon JM, Pohl S, Arnau J. (2018) Secondary metabolite production and the safety of industrially important members of the Bacillus subtilis group. FEMS Microbiol Rev.; 42(6): 721-738.

[55]. Rahman M. (2018). Application of Computational methods in Isolation of plant secondary metabolites, Computational phytochemistry chap 4, ed. Satyajit D. Sarker Lutfun Nahar .107-139.