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PHARMACEUTICAL IMPORTANCE OF PLANT DERIVED BIOMOLECULES AND NATURALLY OCCURRING METABOLITES: AN OVERVIEW

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ABSTRACT

It is well known that plants on the earth are natural source of bioactive compounds. Ancient health system describes diverse group of plant species with their medicinal and therapeutic properties. Plant derived pharmaceutical molecules are the turning to use traditional medicinal systems because phytochemicals are potent source of polyphenols, alkaloids, steroids, vitamins and minerals. However, diverse species of plants on the earth may be exploited to biosynthesized bioactive molecules, vitamins, proteins, carbohydrates and other biologically active polymers for the sustainable and commercial exploitation. Plant derived molecules are converted into committed pharmaceuticals, drugs, antioxidants, feed, food, bio-fuels for the multidimensional industrial processing. In addition to produce large scale pharmaceutically important molecules, several plant biotechnological and genetic approaches are employed to increase the potential and applicability of the plant derived biomolecules for commercialization. We present an overview about the novel studies, issues and importance of plant derived biomolecules and naturally occurring metabolites.

Key words : Biomolecules, bioactive compounds, pharmaceuticals, natural products, medicinal plants, metabolomics.

Introduction

Plant biomolecules are naturally synthesized in the plants and essential for the typical biological process such as morphogenesis, development and cell division (Bunge, 1979). Plant biomolecules includes macromolecules (protein, carbohydrates, lipids, amino acids and nucleic acid) and small molecules like primary metabolites, secondary metabolites and other natural products. Biomolecules are important elements for the living organism on earth; certain biomolecules are usually needed as exogenous biomolecules as nutrient for nourishment to survive in the nature (Voon and Sam, 2019). Most of the biomolecules are organic in nature and chemically composed with carbon, hydrogen, oxygen and nitrogen as major elements. The uniformity of these components in the formation of biomolecules undergoes several metabolic pathways with diverse range of their function in the living organism on the earth (Gayon, 1998). Plants are the important source of the natural remedies as they contain biologically active compounds like polyphenols, terpenic compounds, organic acids, and vitamins (Ramawat *et al.*, 2009). Most of the biologically active compounds are widely occurring groups of phytochemicals (Verpoorte, 2009). Some compounds are not directly involved in the growth and development of plants but have medical property for human health and considered as secondary plant products or plant secondary metabolites.

Plants producing secondary metabolites have historically proven their value as potential source of biomolecules with pharmaceutical and therapeutic potential. In the past decades, pharmaceutical industries mainly concentrated on naturally synthesised compounds for the production of pharmaceutical medicines. Accessibility of plant materials and quantification of the quality inside them have great importance in

pharmaceutical point of view. However, plant materials are often varies on quality and composition and this can hampers the assessment of therapeutic claims. Biochemical composition of plants are not only depends on the identified species but also on the soil mineral composition and the climatic condition under which plants are grown (Bucar *et al*., 2013). Furthermore, during isolation and extraction of bioactive compounds from plant sources are also degraded due to lack of proper extraction protocol and extraction assembly (Jones and Kinghorn, 2012).

Discovery of drugs and pharmaceutically active compounds from plant sources requires multidisciplinary approaches in which compounds are screened and then obtained promising compounds. Importance of the proper selection of initially used pharmacological assay is underlined by the facts that lack of proper clinical efficiency for the detection of desirable compounds form the plant derived sources (Agarwal *et al*., 2014). In addition, failures of novel drug development from plant sources are also considered due to lack of bioassay detection methodology. However, methods for the detection of the activity of bioassay generally based on the simple chemical reaction, such as some widely used techniques to determine the potential antioxidants and their properties form the plant sources (Gulcin, 2012). Modern and traditional trends in medicinal and pharmaceutical industries turn towards using the proactive compounds in the plants without using whole plant as a major source (Veeresham, 2012). Medicinal and aromatic plants are being used for maintenance of human health since ancient time (Petrovska, 2012). In this context, studies have been plant and their particular parts are the riches source of phytochemicals such as alkaloids, phenolic acid, flavonoids that have potential pharmaceutical properties like antioxidant, anti-microbial, anti-fungal and anti-carcinogenic (Wang *et al*., 2017). However, the main components of plants that act as antioxidant are categorized as carotenoids, phenolics and flavonoids. In addition, numbers of chemical compounds have been isolated from plants with excellent antioxidant and other pharmaceutical properties (Yashin *et al*., 2017). Some of the naturally occurring compounds like ascorbic acid, vitamins, polyphenols, carotenoids, gallic acid and other bioactive molecules were found to potentially modulate several kinds of the oxidative stress in human through their free radical scavenging activity (Medhe *et al*., 2014).

Antioxidants produces by plants, prevents oxidative damage in human by neutralizing free radicals and these antioxidants are provided to human as dietary supplements (Salehi *et al*., 2018). In most of the plants and animals, peroxidase, catalase, vitamin C, vitamin E and superoxide dismutase are the potential antioxidants that counter the deleterious effect of the diverse free radicals (Pizzino *et al*., 2017). Furthermore, neutralization mechanism of antioxidants includes prevention, repair and interception. Most of the prevention mechanism is control by SOD, and catalase that inhibit the formation of ROS. SOD converts superoxide to hydrogen peroxide and catalase convert hydrogen peroxide to water, other enzymes are also involve for the repairing of damage (Devasagayam, 2004). On other hand, some antioxidants including vitamin A, vitamin C, vitamin K, vitamin E, polyphenols, uric acid, and carotenes are non-enzymes (Ramana *et al*., 2018). In addition, ascorbic acid and their derivatives reduce the membrane bound tocopherol and quickly generate active form of tocopherol that is able to scavenge free radicals (Pisoschi and Pop, 2015). The antioxidants from natural sources have strong potential to eliminate acute oxidative stress and also able to maintain cellular homeostasis through free radical scavenging, prevention of lipid peroxidation and also inhibit the formation of unwanted radicals (Palace *et al*., 1999).

Recent research and development indicated that use of traditional medicinal and aromatic plants including the plants rather than medicinal classification accounts for lower incidence of the several diseases that occur in human and animal (Ozkan *et al*., 2016). A number of plants have been investigated and identified as with potential pharmaceutical and antioxidant properties (Panche *et al*., 2016). Important plant secondary metabolite sources like phenolic acid accounts for colour antioxidant property and other important sensory quality of the plants. Phenolic acid produced in plants are used as protective agents against, viruses, bacteria, fungus and other radioactive radiations (Heleno *et al*., 2015).

In this review, we have elaborated the various scientific interests in the plant-derived natural product based pharmaceutical drug discovery with potential technological advantages in the relevant field, also included the better understanding of the screening methodologies and analytical techniques for optimization of natural leads using synthetic modification strategies.

Naturally derived drugs from plant sources

Discovery of biomolecules and medicinal drugs from plant sources started at the beginning of 19th century, when the German apothecary assistant Friedrich Serturner succeeded in isolating the analgesic and sleep-inducing agent from opium which he named *morphium* (morphine) after the Greek god of dreams, Morpheus

(Serturner, 1817). After the discovery of Penicillin in 1928, an era of drug discovery from microbial sources was initiated in 1930th with scientific foundation of modern pharmaceutical just after the Second World War. During that time pharmaceutical use of naturally extracted plant extract was used as pure compounds for various type of treatment (David *et al.*, 2015). Numbers of challenges related with use of plants as a source for identification of bioactive compound are related with accessibility of desired plant materials (Bucar *et al.*, 2013). Although, number of plat derived natural products have been identified and successfully isolated and also tested for their wade range of biological activities (Kinghorn *et al.*, 2011). In addition, some plant materials are initially required for the pharmaceutical characterization and evaluation for their activity and potentiality in the treatment. Due to limited availability of the plant derived natural bioactive compounds is identified as promising bioactivity and have been emerged as pharmaceutical lead (Cragg and Newman, 2013).

Furthermore, habitat of plants, particularly wild species can rapidly disappear as anthropic pressure for the strategic drug and pharmaceutical product development (David *et al*., 2015). In most of the cases of plant materials and the array of entire additional factors affect its accessibility such as local wars, change in the regulation of cross-border, export of plant materials etc. However, the importance of plant materials accessibility has illustrated in the recent study by Amirkia and Heinrich (2014) with aim of investigation and proper correlation between several species of alkaloids and their occurrence with proper use as pharmaceutical drugs. The findings of Amirkia and Heinrich (2014) accessed on the basis of Global Biodiversity Information Facilities (GBIF) data and they found that more than 90% of the alkaloids used in medicine with more than 50 occurrences in the GBIF database and only few have less than 10 occurrences.

Therefore, it is concluded that the natural products of the plant sources occurring in many species are more variable for medicinal therapeutic use and also for are the major obstacle of the success in the development and commercialization of the natural plant products (Kingston, 2011). In this context, better appreciation of the advantages of the natural products and emerging interest in plant derived natural product based pharmaceutical drug discovery could increase in the number of scientific studies.

Heterogeneous production of drugs from plant source

Heterogeneous synthesis of plant derived natural products and bioactive compounds are the major goal of pharmaceutical drug development for the human health (Ongley *et al*., 2013). In this context, reconstitution of the beneficial compounds must be targeted for the strategic biosynthesis in foreign host in order to increase the yield of beneficial biosynthetic products (Marienhagen and Bott, 2013). Such type of practices for the production of heterogeneous drugs from the plant sources are the alternative source of biosynthetic drug production rather than traditional source of drug production (Howat *et al*., 2014). Potential constitution with respect to biosynthetic

Table 1 : List of the plant derived pharmaceutical compounds.

Year of introduction	Plant source	Name of compound	Action mechanism
1987	*Artemisia annua* L.	Arteminism	Radical formation
1989	*Solanum* spp.	Nanoxel*c*	Apoptosis triggering
1993	*Taxus brevifolia* Nutt	Paclitaxel	Cancer chemotherapy
1999	Artemisia galbella	Arglabin	Chemotherapy and cancer treatment
2001	*Galanthus caucasicus*	Galanthamine	Alzheimer's disease
2005	*Cannabis sativa* L.	Dronabinol	Receptor activator and Chronic neuropathic pain
2005	*Solanum* spp.	Taxol	Mitotic inhibitor
2007	*Taxus brevifolia* Nutt	Abraxane*c*	Cancer chemotherapy
2009	*Colchicum* spp.	Colchicine	tubulin binding
2010	*Capsicum annum* L	Capsaicin	Activator and Post-herpetic neuralgia
2012	*Euphorbia peplus*L.	Ingenolmebutate	inducer of cell death
2012	*Cephalotaxus harringtonia*	Homoharringtonine	Oncology (protein translation inhibitor

Source: Butler *et al.* (2014)

pathway for the production of active compounds from the heterogeneous plant sources also requires heterogeneous host with proper information about the involved enzymes and genes coding them (Miralpeix *et al*., 2013). Regulation of genes and their compartmentalization needs to be isolated from their native source and also their mobilization into heterogeneous host through appropriate vector. Therefore, choice of the potential and appropriate host system is very important for the strategic production of pharmaceutically important drugs (Chen *et al*., 2013). Some microbial hosts like *Saccharomyces cerevisiae* and *Escherichia coli* have been widely used for the commercial production of the plant derived pharmaceutically important compounds. In this context, some non-pathogenic microorganisms have also been utilized for the industrial fermentation and have served as model for the fundamental research of molecular biology as well as genetic manipulation (Siddiqui *et al*., 2012). However, some microbial host like *E. coli* fails to perform post-transcriptional modification because of the narrow genetic base (Zhang *et al*., 2008). Furthermore, implementation of some complicated eukaryotic enzymes like cytochrome P-450s contains several types of enzyme of the plant secondary metabolite biosynthesis and are tightly attached to the endoplasmic reticulum of the eukaryotic cells (Wang *et al*., 2011). Some plant-based expression systems including transgenic cell suspension culture, hairy root culture, have been successfully used for the strategic production of diverse plant secondary metabolites (Vasilev *et al*., 2014). On other hand, some important plant secondary metabolites to produce in the microbial system and tissue culture can be produce in the intact heterologous plants (Wilson and Roberts, 2012).

Renewal of natural product based drug

Knowledge of medicinal and pharmaceutical plants for the drug discovery and pharmaceutical use are mainly based on the Roman and Greek culture. Natural population of the diverse group of medicinal plants species have been facing pressure from human induced factors like deforestation, environmental damage, climate change, development of land for agricultural production and industrialization (Arora *et al*., 2010). In fact, more than 25 % of the global aromatic and medicinal plants species are threatened to varying degree (Schippmann *et al*., 2006). However, two third of the medicinal and aromatic plant species are collected from wild sources and local habitats for the extraction of pharmaceutically important drugs (Canter *et al*., 2005). Furthermore, the renewal of natural products from medicinal and aromatic plants needs the domestication of natural plant vegetation for the strategic identification and isolation of important drugs. Isolation of natural products from plant species often acceptable if moderate amount of respective compounds is pharmaceutically needed. Another strategic aspect related to renewal of natural products and their identification with respect to pharmaceutical drug and bioactive compounds increasingly recognize the some plant derived natural products that needs to re-stabilize *in vitro* condition with the interference of microbial organism in order to produce pharmaceutically active molecules (Tomas-Barberan *et al*., 2014). Furthermore, an emerging concepts for the renewal of natural products termed as metabolism-directed approach is able to address the challenges through the proper use of *in vivo* and *in vitro* techniques of mass multiplication of plants with talented search plants with pharmaceutical importance (Yu *et al*., 2014). Therefore, the bioactivity of the plants extract may be responsive result of several components of potential compounds for the synergetic interaction and natural product isolation (Akao *et al*., 2002).

Strategic selection of pharmaceutically actives plant compounds

Random screening approach of the plants with pharmaceutical and bioactive compound has been used by the researches since more than eight decades for the extraction active molecules (Henrich and Beutler, 2013). The random selection of plant materials has the potential in the identification of bioactivities and could not been predicted based on the existing knowledge. Moreover, the uses of pharmacological assay have medium-throughput are often available in the very small quantity that limits the number of bioassay in which they can be tested for bioactive molecules (Barbosa *et al*., 2012). Some prominent evidences that have been approved by the drug research societies were initially discovered by the use of previous pharmaceutical data and are served as lead compound for the development of number of bioactive compounds like sodium salt, chromoglicic acid in the treatment of allergy and asthma (Cragg and Newman, 2013). In addition, some other important molecules like papaverine was the basis for development of buguanidine type drug development, quinine for malaria and other potent drugs from plant sources (White, 2008). Depending on the diverse nature of drug producing plants various kind of information can be acquired from the different sources and review articles on the pharmaceutically important plants used in the strategic selection for the development of desirable drugs for the number of diseases in the human beings (Leonti, 2011). Therefore, testing of the diverse plant species and varieties can be applied to increase the probability of the

Table 2 : Selection of plant materials for discovery of bioactive compounds.

Desirable features	Strategic approaches	References
Random selection of extracts from different plant species, enriched fractions, or isolated natural products	Random approach	Gyllenhaal *et al*. (2012), Fakhrudin *et al*. (2014)
Selection of the test samples based on traditional medicinal applications of the plant species	Ethno-pharmacological approach	Siriwatanametanon and Heinrich (2011)
Selection of the test samples based on chemotaxonomy and phylogeny taking into account that plant species from some genera or families are known to produce compounds	Chemosystematic approach	Alali *et al*. (2008), Cook *et al*. (2014)
Compound classes associated with a certain bioactivity or therapeutic potential.	Chemosystematic approach	Obbo *et al*. (2013), Thoppil *et al*. (2013)
Selection of test samples based on the interactions between organisms and their environment	Ecological approach	Zhao and Brinton (2005), Guasch *et al*. (2012)
Plant secondary metabolites possess ecological functions from which a potential therapeutic use for humans can be derived	Ecological approach	Grienke *et al*. (2014), Waltenberger *et al*. (2011)
Selection of test samples relying on *in silico* bioactivity predictions for constituents of certain plant species.	Computational approach	Sathishkumar *et al*. (2013), Noreen *et al*. (1998)

identification of relevant bioactive compounds from the least number of plant samples with using limited number of pharmaceutically important assays (Heinrich, 2010).

Identification of bioactive compounds

Identification of bioactive compounds from the diverse group of plant species is one of the important practices in the field of the identification of pharmaceutically important and drug industry (Soejarto *et al*., 2004). Important challenges related to use of plants as a source for the identification of bioactive molecules are related with accessibility of the diverse group of plant species (Oliva, 2011). If the variability of the number of plant species is less then change of the availability of the natural plant products must be less (Gilbert, 2010). Sometimes, limited amount of plant materials are usually required for the initial pharmacological evaluation because of the known and identified bioactive compounds from the known plant sources (Li and Vederas, 2009). Furthermore, limited availability of the bioactive plant derived natural products is identified to have very promising bioactivity and becomes a drug delivery leader. Collection and evaluation of plant species from the wild source can rapidly increase the rate of the identification of bioactive molecules with desirable pharmaceutical traits (Appendino *et al*., 2010). Therefore, cultivation of identified lines from the wilds plant source may provide strong platform in the field of drug industry for the commercialization of bioactive compounds. In number of cases, when a plant species is identified for the particular bioactive compounds and commercialized for the production of herbal medicine then its constituents used as pharmaceutical drug and ultimately become threatened because of the extensive wild-crafting and unsustainable harvesting approaches (Ortholand and Ganesan, 2004). In this context, identification and quantification of bioactive compounds from the plant extracts are generally complicated and challenging because of the diverse chemical and physical properties as well as wide range of the concentration gradients (Kjer *et al*., 2010). Therefore, highly sophisticated and reproducible analytical methods like high performance liquid chromatography, gas chromatography and other spectroscopic techniques applied for the strategic identification and extraction of bioactive compounds with pharmaceutical importance (Greek *et al*., 2011). Potential applications of biotechnological tools and techniques for the identification of bioactive compounds from plant source are also helpful. Furthermore, some advance techniques of the molecular biology and genetic engineering like marker-assisted selection (MAS), genome-wide association studies (GWAS) and Cas-based CRISPR techniques of the genome edition may also helpful for the improvement of traits in the plant species

Table 3 : Bioactive compounds and their effectiveness.

Bioactive molecules	Targeted molecules	Preventive effects
Trihydroxyisoflavone	PI3 K Cyclin-dependent kinase 2	EGF-induced cell proliferation and transformation
Caffeic acid	FYN	UVB-induced COX2 expression
Gingerol	Leukotriene A4 hydrolase (LTA4H)	Xenograft tumour volume of human HCT116 colon cancer cells
Cyanidin	RAF Mitogen-activated protein kinase kinase 4 (MKK4) MEK1	UVB-induced COX2 expression
Cryptotanshinone	Signal transducer and activator of transcription 3	Human prostate cancer cell proliferation
Delphinidin	FYN RAF,MEK1,ERKs,MKK4 PI3K	TNF-induced COX2 expression TPA-induced cell transformation UVB-induced COX2 expression
Epigallocatechin gallate	FYN Insulin-like growth factor-1 receptor Glucose-regulated protein 78	Etoposide-induced breast cancer cell death and drug resistance
	Heat shock protein 90	TCDD-mediated gene induction in hepatoma cells
	-chain-associated protein kinase70	Leukaemia proliferation
	RasGTPase activating protein SH3 domain binding protein 1	Anchorage-independent growth of human and mouse lung cancer cell lines
Equol	MEK1	TPA-induced cell transformation
Fisetin	CDK6	Kinase activity
Kaempferol	SRC	UVB-induced two stage skin

Source: Manas Kumar *et al.* (2012)

for the special purpose of drug production (Bevan *et al*., 2017; Hurgobin *et al*., 2018). In addition, potential application of the plant molecular farming for the production of desirable drug and pharmaceutically important molecules has been employed the workers for the alternation of plant genomes with desirable purpose (Drake*et al*., 2009; Valkova *et al*., 2013).

Organic synthesis of plant derived compounds

Plant produces wide range of volatile organic compounds including most of the secondary metabolites like isoprene, alkaloids, phenolics, terpenoids and well known oxygenated compounds such as carboxylic acid, alcohol and aldehydes (Nicolaou *et al*., 1998). In last two decades, progress has been made regarding the elucidation of the metabolic pathways for the strategic production of plant derived organic compounds with pharmaceutical importance. Therefore, strategy of natural product synthesis are not directly depends on the various types of chemical reaction, although the synthesis of most if the natural plant products oriented on the basis of central steps carryout by the plant under favourable condition (Furstner, 2011). Most of the organic synthesis strategies may be built on the interference of important intermediates and precaursor compounds (Corey and Cheng, 1989). In this context, identification of strategies and approaches in the organic synthesis planning could must be applied all types of precaursor and catalytic intermediates for the conversion of precaursor materials in to the final products with number of pharmaceutical importance (Han *et al*., 2014).

Some of the specific instances in terms of natural product biosynthesis have at least one key step which emulates the effort to render the biosynthesis of final product with strong efficiency (Bulger *et al*., 2008). Notably, collective approaches of the organic synthesis focused on the structurally diverse natural products from the plant source that can demonstrate various kinds of plant alkaloids with potential of drug and pharmaceutical importance. The collective approaches may also led to the preparation of variety of plant derived alkaloids through the key intermediate precaursor have also been support the organic biosynthesis rationales (Cannon and Overman, 2012). Thus, collective organic synthesis has given rise to numerous natural products with pharmaceutical importance and also for the commercial exploitation of drug production (Ghavimi and Magnus, 2014).

Conclusion and Future Prospects

Plants are the richest source of biomolecules and

proven their value as a source of pharmaceutical molecule with therapeutical potential. Developed countries are turning to use traditional medicine system that involves the diverse group of plant species as herbal drugs. It is estimated that plant derived biomolecules make – up a potential segment of the natural product based pharmaceutically important compounds. Most of the plant families produce secondary metabolites including nitrogen containing alkaloids have contributed the largest number of drugs ranging with broad capacities of health promoting bioactive compounds. The goal and future prospects of plants as source of bioactive molecules to isolate pharmaceutically important compounds for the direct use as drugs like digoxin, digitoxin, morphine, reserpine, taxol, vinblastine, vincristine to produce bioactive compounds for semi-synthesis to produce patentable entities of higher activity and lower toxicity.

References

Agarwal, A., D'Souza P., Johnson T.S., Dethe S.M. and Chandrasekaran C. (2014). Use of *in vitro* bioassays for assessing botanicals. *Curr. Opin. Biotechnol*. **25**, 39–44.

Akao, T., Yoshino T., Kobashi K. and Hattori M. (2002). Evaluation of salicin as an antipyretic prodrug that does not cause gastric injury. *Planta Med*. **68**, 714–718.

Amirkia, V. and Heinrich M. (2014). Alkaloids as drug leads — a predictive structural and biodiversity-based analysis. *Phytochem. Lett.*, **10**, xlviii–liii.

Appendino, G., Fontana G. and Pollastro F. (2010). Natural products drug discovery. In: Liu, H.-W. and Mander L. (eds). Comprehensive Natural Products II. Elsevier; Oxford: p. 205-236.

Arora R., Mathur A. and Mathur A.K. (2010). Emerging trends in medicinal plant biotechnology. *Medicinal Plant Biotechnol.*, 1–12.

Barbosa, W.L.R., do Nascimento M.S., do Nascimento, Pinto L., Maia F.L.C., Sousa A.J.A. and Silva Júnior J.O.C. (2012). Selecting Medicinal Plants for Development of Phytomedicine and Use in Primary Health Care, Bioactive Compounds in Phytomedicine. Rasooli, Iraj, editor. InTech. ISBN: 978-953-307-805-2.

Bevan, M.W., Uauy C., Wulff B.B., Zhou J., Krasileva K. and Clark M.D. (2017). Genomic innovation for crop improvement. *Nature*, **543**, 346–354.

Bucar, F., Wube A. and Schmid M. (2013). Natural product isolation — how to get from biological material to pure compounds. *Nat. Prod. Rep*., **30**, 525–545.

Bulger, P.G., Bagal S.K. and Marquez R. (2008). Recent advances in biomimetic natural product synthesis. *Nat. Prod. Rep*., **25**, 254–297.

Bunge, M. (1979). *Treatise on Basic Philosophy*. vol. 4. Ontology II: A World of Systems.61-2.

Cannon, J.S. and Overman L.E. (2012). Is there no end to the total syntheses of strychnine? Lessons learned in strategy and tactics in total synthesis. *Angew. Chem. Int. Ed. Engl*., **51**, 4288–4311.

Canter, P.H., Thomas H. and Ernst E. (2005). Bringing medicinal plants into cultivation: opportunities and challenges for biotechnology. *Trends Biotechnol.*, **23**, 180–185.

Chen, X., Zhou L., Tian K., Kumar A., Singh S. and Prior B.A. (2013). Metabolic engineering of *Escherichia coli*: A sustainable industrial platform for bio-based chemical production. *Biotechnol. Adv.*, **31**, 1200–1223.

Cook, D., Lee S.T., Taylor C.M., Bassuner B., Riet-Correa F. and Pfister J.A. (2014). Detection of toxic monofluoroacetate in *Palicourea* species. *Toxicon*., **80**, 9–16.

Corey, E.J. and Cheng X.M. (1989). *The Logic of Chemical Synthesis*. Wiley; New York.

Cragg, G.M. and Newman D.J. (2013). Natural products: a continuing source of novel drug leads. *Biochim. Biophys. Acta*, **1830**, 3670–3695.

David, B., Wolfender J.L. and Dias D.A. (2015). The pharmaceutical industry and natural products: historical status and new trends. *Phytochem. Rev.*, **14(2)**, 299–315.

Devasagayam, T.P.A., Tilak J.C., Boloor K.K., Sane K.S., Ghaskadbi S.S. and Lele R.D. (2004). Free radicals and antioxidants in human health: current status and future prospects. *J. Assoc. Physicians India*, **52**, 794-804.

Drake, P.M., Barbi T., Sexton A., Mcgowan E., Stadl-mann J., Navarre C. and Ma J.K.C. (2009). Development of rhizosecretion as a production system for recombinant proteins from hydroponic cultivated tobacco. *The FASEB J*., **23**, 3581–3589.

Fakhrudin, N., Waltenberger B., Cabaravdic M., Atanasov A.G., Malainer C. and Schachner D. (2014). Identification of plumericin as a potent new inhibitor of the NF-kappaB pathway with anti-inflammatory activity *in vitro* and *in vivo*. *Br. J. Pharmacol*., **171**, 1676–1686.

Furstner, A. (2011). Metathesis in total synthesis. *Chem. Commun*. (Camb.), **47**, 6505–6511.

Gayon, J. (1998). La philosophie et la biologie. In : Mattei, J.F. (ed.). *Encyclopedie philosophique universelle*. vol. **IV**, Le Discours philosophique. Presses Universities de France. pp. 2152–2171.

Ghavimi, B. and Magnus P. (2014). Total synthesis of 8,14-dihydromorphinandienone alkaloids. *Org. Lett*., **16**, 1708–1711.

Alali, F.Q., Gharaibeh A., Ghawanmeh A., Tawaha K. and Oberlies N.H. (2008). Colchicinoids from *Colchicum crocifolium* Boiss.: A case study in dereplication strategies for (–)-colchicine and related analogues using LC–MS and LC–PDA techniques. *Phytochem. Anal*., **19**, 385–394.

Gilbert, N. (2010). Biodiversity law could stymie research. *Nature*, **463**, 598.

Greek, D.J., Jankevics A., Breitling R., Watson D.G., Barrett M.P. and Burgess K.E. (2011). Toward global

metabolomics analysis with hydrophilic interaction liquid chromatography-mass spectrometry: Improved metabolite identification by retention time prediction. *Anal. Chem*., **83**, 8703–8710.

Grienke, U., Braun H., Seidel N., Kirchmair J., Richter M. and Krumbholz A. (2014). Computer-guided approach to access the anti-influenza activity of licorice constituents. *J. Nat. Prod.*, **77**, 563–570.

Guasch, L., Ojeda M.J., Gonzalez-Abuin N., Sala E., Cereto-Massague A. and Mulero M. (2012). Identification of novel human dipeptidyl peptidase-IV inhibitors of natural origin (part I): virtual screening and activity assays. *PLoS One*, **7**, e44971.

Gulcin, I. (2012). Antioxidant activity of food constituents: an overview. *Arch. Toxicol*., **86**, 345–391.

Gyllenhaal, C., Kadushin M.R., Southavong B., Sydara K., Bouamanivong S. and Xaiveu M. (2012). Ethnobotanical approach *versus* random approach in the search for new bioactive compounds: support of a hypothesis. *Pharm. Biol*., **50**, 30–41.

Han, J.C., Li F. and Li C.C. (2014). Collective synthesis of humulanolides using a metathesis cascade reaction. *J. Am. Chem. Soc*., **136**, 13610–13613.

Heinrich, M. (2011). Ethno pharmacology in the 21st century — grand challenges. *Front. Pharmacol*., **1**, 8.

Heinrich, M. (2010). Ethnopharmacology and drug discovery. In: Liu, H.-W. and Mander L. (eds). *Comprehensive Natural Products II*. Elsevier; Oxford: p. 351-381.

Heleno, S.A., Martins A., Queiroz and Ferreira I.C. (2015). Bioactivity of phenolic acids: metabolites versus parent compounds: A review. *Food Chem*., **173**, 501-513.

Henrich, C.J. and Beutler J.A. (2013). Matching the power of high throughput screening to the chemical diversity of natural products. *Nat. Prod. Rep*., **30**, 1284–1298.

Howat, S., Park B., Oh I.S., Jin Y.W., Lee E.K. and Loake G.J. (2014). Paclitaxel: biosynthesis, production and future prospects. *N. Biotechnol*., **31**, 242–245.

Hurgobin, B., Golicz A.A., Bayer P.E., Chan C.K.K., Tirnaz S. and Dolatabadian A. (2018). Homoeologous exchange is a major cause of gene presence/absence variation in the amphidiploid *Brassica napus*. *Plant Biotechnol. J*., **16**, 1265–1274.

Jones, W.P. and Kinghorn A.D. (2012). Extraction of plant secondary metabolites. *Methods Mol. Biol*., **864**, 341–366.

Kinghorn, A.D., Pan L., Fletcher J.N. and Chai H. (2011). The relevance of higher plants in lead compound discovery programs. *J. Nat. Prod*., **74**, 1539–1555.

Kingston, D.G. (2011). Modern natural products drug discovery and its relevance to biodiversity conservation. *J. Nat. Prod*., **74**, 496–511.

Kjer, J., Debbab A., Aly A.H. and Proksch P. (2010). Methods for isolation of marine-derived endophytic fungi and their bioactive secondary products. *Nat. Protoc*., **5**, 479–490.

Leonti, M. (2011). The future is written: impact of scripts on the cognition, selection, knowledge and transmission of medicinal plant use and its implications for ethnobotany and ethnopharmacology. *J. Ethnopharmacol*., **134**, 542–555.

Li, J.W. and Vederas J.C. (2009). Drug discovery and natural products: end of an era or an endless frontier? *Science*, **325**, 161–165.

Manas, K., Mukhopadhyay P. and Banerjee D.N. (2012). Phytochemicals – biomolecules for prevention and treatment of human diseases-a review. Int. *J. Scient. Engg Res*., **(3)- 7**, 1- 33.

Marienhagen, J. and Bott M. (2013). Metabolic engineering of microorganisms for the synthesis of plant natural products. *J. Biotechnol*., **163**, 166–178.

Medhe, S., Bansal P. and Srivastava M.M. (2014). Enhanced antioxidant activity of gold nanoparticles embedded 3, 6-dihydroxyflavone: A combinational study. *Appl. Nanosci.*, **4**, 153–161.

Miralpeix, B., Rischer H., Hakkinen S.T., Ritala A., Seppanen-Laakso T. and Oksman-Caldentey K.M. (2013). Metabolic engineering of plant secondary products: which way forward? *Curr. Pharm. Des*., **19**, 5622–5639.

Nicolaou, K.C., Sorensen E.J. and Winssinger N. (1998). The art and science of organic and natural products synthesis. *J. Chem. Educ*., **75**, 1226–1258.

Noreen, Y., el-Seedi H., Perera P. and Bohlin L. (1998). Two new isoflavones from *Ceibapentandra* and their effect on cyclooxygenase-catalyzed prostaglandin biosynthesis. *J. Nat. Prod*., **61**, 8–12.

Obbo, C.J.D., Makanga B., Mulholland D.A., Coombes P.H. and Brun R. (2013). Antiprotozoal activity of *Khayaanthotheca* (Welv.) C.D.C. a plant used by chimpanzees for self-medication. *J. Ethnopharmacol*., **147**, 220–223.

Oliva, J. (2011). Sharing the benefits of biodiversity: a new international protocol and its implications for research and development. *Planta Med*., **77**, 1221–1227.

Ongley, S.E., Bian X., Neilan B.A. and Muller R. (2013). Recent advances in the heterologous expression of microbial natural product biosynthetic pathways. *Nat. Prod. Rep*., **30**, 1121–1138.

Orthol, J.Y. and Ganesan A. (2004). Natural products and combinatorial chemistry: Back to the future. *Curr. Opin. Chem. Biol*., **8**, 271–280.

Ozkan, G., Kamiloglu S., Ozdal T., Boyacioglu D. and Capanoglu E. (2016). Potential use of turkish medicinal plants in the treatment of various diseases. *Molecules*, **21(3)**, 257.

Palace, V.P., Khaper N., Qin Q. and Singal P.K. (1999) Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. *Free Radic. Biol. Med*., **26(5-6)**, 746-761.

Panche, A.N., Diwan A.D. and Chandra S.R. (2016). Flavonoids: an overview. *J. Nutr. Sci*., **5**, e47.

Petrovska, B.B. (2012). Historical review of medicinal plants' usage. *Pharmacogn Rev*., **6(11)**, 1–5.

Pisoschi, A.M. and Pop A. (2015). The role of antioxidants in the chemistry of oxidative stress: A review. *Eur. J. Med. Chem*., **97**, 55-74.

Pizzino, G., Irrera N., Cucinotta M., Pallio G., Mannino F., Arcoraci V., Squadrito F., Altavilla D. and Bitto A. (2017). Oxidative Stress: harms and benefits for human health. *Oxid. Med. Cell Longev*., **3**, 1-13.

Ramana, K.V., Reddy A.B.M., Majeti N.V.R.K. and Singhal S.S. (2018). Therapeutic potential of natural antioxidants. *Oxid. Med. Cell Longev*., 9471051. doi: 10.1155/2018/ 9471051.

Ramawat, K., Dass S. and Mathur M. (2009). The chemical diversity of bioactive molecules and therapeutic potential of medicinal plants. In: *Herbal drugs: Ethnomedicine to modern medicine*, Springer: pp 7 32.

Salehi, B., Martorell M., Arbiser J.L., Sureda A., Martins N., Maurya P.K., Sharifi-Rad M., Kumar P. and Sharifi-Rad J. (2018). Antioxidants: positive or negative actors. *Biomolecules*, **8(4)**, 114-124.

Sathish, Kumar N., Karpagam V., Sathiyamoorthy S., Woo M.J., Kim Y.J. and Yang D.C. (2013). Computer-aided identification of EGFR tyrosine kinase inhibitors using ginsenosides from *Panax ginseng*. *Comput. Biol. Med*., **43**, 786–797.

Schippmann, U., Leaman D. and Cunningham A.B. (2006). A comparison of cultivation and wild collection of medicinal and aromatic plants under sustainability aspects. In: Bogers, R.J., C.L.E. Lange D. (eds). *Medicinal and Aromatic Plants: Agricultural, Commercial, Ecological, Legal, Pharmacological and Social Aspects*. Springer; Dordrecht. p. 75-95.

Serturner, F.W. (1817). Uber das Morphium, eineneuesalzfähige Grundlage, und die Mekonsaure, alsHauptbestandteile des Opiums. *Ann. Phys*., **25**, 56–90.

Siddiqui, M.S., Thodey K., Trenchard I. and Smolke C.D. (2012). Advancing secondary metabolite biosynthesis in yeast with synthetic biology tools. *FEMS Yeast Res*., **12**, 144–170.

Siriwatanametanon, N. and Heinrich M. (2011). The Thai medicinal plant *Gynura pseudochina* var. *hispida*: chemical composition and *in vitro* NF-kappaB inhibitory activity. *Nat. Prod. Commun*., **6**, 627–630.

Soejarto, D.D., Gyllenhaal C., Fong H.H., Xuan L.T., Hiep N.T. and Hung N.V. (2004). The UIC ICBG (University of Illinois at Chicago International Cooperative Biodiversity Group) Memorandum of Agreement: a model of benefit-sharing arrangement in natural products drug discovery and development. *J. Nat. Prod*., **67**, 294–299.

Thoppil, R.J., Harlev E., Mandal A., Nevo E. and Bishayee A. (2013). Antitumor activities of extracts from selected desert plants against HepG2 human hepatocellular carcinoma cells. *Pharm. Biol*., **51**, 668–674.

Tomas-Barberan, F.A., Garcia-Villalba R., Gonzalez-Sarrias A., Selma M.V. and Espin J.C. (2014). Ellagic acid metabolism by human gut microbiota: consistent observation of three urolithin phenotypes in intervention trials, independent of food source, age and health status. *J. Agric. Food Chem*., **62**, 6535–6538.

Valkova, R., Apostolova E. and Naimov S. (2013). Plant molecular farming: opportunities and challenges. *J. Serbian Chem. Soc*., **78**, 407415.

Vasilev, N., Schmitz C., Dong L., Ritala A., Imseng N. and Häkkinen S. (2014). Comparison of plant-based expression platforms for the heterologous production of geraniol. *Plant Cell Tissue Organ Cult*. **117**, 373–380.

Veeresham, C. (2012). Natural products derived from plants as a source of drugs. *J. Adv. Pharm. Technol. Res*., **3(4)**, 200-201.

Verpoorte, R. (2009). Medicinal plants: A renewable resource for novel leads and drugs. In : *Herbal drugs: Ethnomedicine to modern medicine*, Springer: pp 1 5.

Voon, C.H. and Sam S.T. (2019). "Biosensors". Nanobiosensors for Bimolecular Targeting. Elsevier.

Waltenberger, B., Schuster D., Paramapojn S., Gritsanapan W., Wolber G. and Rollinger J.M. (2011). Predicting cyclooxygenase inhibition by three-dimensional pharmacophoric profiling. Part II: Identification of enzyme inhibitors from Prasaplai, a Thai traditional medicine. *Phytomedicine*, **18**, 119–133.

Wang, R., Xiao S. and Niu Z. (2017). Anti-cancer activity of *Aster tataricus*on ON SCC-9 human oral squamous carcinoma. *Afr. J. Tradit. Complem. Altern. Med.*, **14 (2)**, 142–147.

Wang, Y., Chen S. and Yu O. (2011b). Metabolic engineering of flavonoids in plants and microorganisms. *Appl. Microbiol. Biotechnol.*, **91**, 949–956.

White, N.J. (2008). Qinghaosu (artemisinin): The price of success. *Science*, **320**, 330–334.

Wilson, S.A. and Roberts S.C. (2012). Recent advances towards development and commercialization of plant cell culture processes for the synthesis of biomolecules. *Plant Biotechnol. J*., **10**, 249–268.

Yashin, A.,Yashin Y., Xia X. and Nemzer B. (2017). Antioxidant activity of spices and their impact on human health: A Review. *Antioxidants (Basel)*, **6(3)**, Pii: E70.

Yu, L., Huang H., Yu L.L. and Wang T.T. (2014). Utility of hesperidinase for food function research: enzymatic digestion of botanical extracts alters cellular antioxidant capacities and anti-inflammatory properties. *J. Agric. Food Chem*., **62**, 8640–8647.

Zhang, H., Wang Y. and Pfeifer B.A. (2008). Bacterial hosts for natural product production. *Mol. Pharm*., **5**, 212–225.