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REVIEW

Functional Diversity of Plant Metabolome and Microbiome in Health Services to the Human Life

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Abstract The basic attribute that differentiates animals and plants apart from their established biological differences and photosynthesis is that the former tend to escape from vagaries of nature to protect themselves "physically" whereas the latter being immobile (anchored in soil) have the only choice to face the adversities on their stride, "chemically". In philosophical terms this also teaches us a biological strategy that the best way to face challenges in life is to face, respond with activity (metabolic) and cope with them so as to turn them into capabilities (biological functions). The plants have acquired this capability by evolving in such a way through phytomolecules through a flexible functional metabolome that caters to their ever-changing demands for survival and existence. The best models to study the functional diversity of plant metabolomes are the non-model medicinal and aromatic plants. This paper discusses functional diversity of plant metabolomes *vis-à-vis* their utility for mankind in tangible terms through illustrative case studies. Humans ($\sim$100 trillion cells) on the other hand are merely 10 % of their own in terms of genome or metabolome being dependent on 90 % of the cells that are in and on them of the microflora that determines human health and performance through a unique colonization and balance of populations in the gut or GI tract.

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Introduction

"Plants do not speak, they just whisper! Therefore, you have to be real close to them to understand them!!"—derived from Dr. Norman E. Borlaug (March 25, 1914–September 12, 2009).

Plants represent the biggest treasure of natural products that carry the potential to provide novel drugs and nutraceuticals. Today many of the commercially used pharmaceuticals/therapeutics and functional foods are either themselves products of plant secondary metabolism or owe their origin to phytomolecules, thereby justifying the terms "Phytoceuticals" and "Nutraceuticals", which refer to pharmaceutical or nutritional values of these plant compounds, respectively. Most of these molecules (phytoceuticals/nutraceuticals) belong to one of the following classes of secondary metabolites—terpenoids, alkaloids, glycosides, phenylpropanoids or complexes of these [1]. Medicinal and Aromatic Plants (MAPs) cater to the two largest industries serving mankind—pharma and healthcare on one hand and the aroma (encompassing a host of industries like perfumery, cosmetics, toiletries, food and beverages) on the other [2]. Although it is really difficult to deny any plant on the face of the earth, the status of a medicinal plant, some plants have been particularly classified into this category due to the specific properties possessed by the secondary metabolites produced by them. The secondary metabolite biosynthetic pathways operating in each MAP are normally proficient in the biosynthesis of one of the classes of secondary metabolites, which in turn

Table 1 Plant sources for some important categories of therapeutic agents

S. No.	Therapeutic category	Plant sources possessing the metabolites (bioactive phytomolecules)
1	Nervine tonics	*Asparagus racemosus* (saponins), *Acorus calamus* (phenylpropanoids), *Withania somnifera* (alkaloids), *Bacopa monnieri* (triterpenoid saponins), *Centella asiatica* (triterpenoid saponins), *Nelumbo nucifera* (alkaloids)
2	Anti-obesity	*Ephedra sinica* (alkaloids ephedrine and pseudoephedrine), *Garcinia cambogia* (hydroxycitric acid), *Hypericum perforatum* (Hypericin, polycyclic quinone), *Malus x domestica* or red apple (pyruvate), *Commiphora wightii* (steroid, gugglesterone), *Saccharum officinarum* (policosanol), *Camellia sinensis* (flavanoid, caffeine), *Allium sativum* (alicin or diallyl thiosulfinate)
3	Anti-diabetes	*Momordica charantia* (seed extract protein *p*-insulin), *Coccinia indica* (triterpenoid, taraxerone), *Gymnema sylvestre* (Gymnema saponin), *Pterocarpus marsupium* (flavonoid), *Lagerstroemia speciosa* (triterpenoids, corosolic acid), *Trigonella foenum-graecum* (alkaloids, trigonelline and choline), *Stevia rebaudiana* (stevioside, diterpene glycoside), *Tinospora cordifolia* (tinosporin, cordifolide, diterpene)
4	Anti-cancer	*Colchicum autumnale* (alkaloid colchicine), *Betula alba* (triterpene betulinic acid), *Camptotheca acuminata* (alkaloid camptothecin), *Cannabis sativa* (sesquiterpene tetrahydrocannabinol), *Podophyllum hexandrum* (lignan podophyllotoxin), *Nothapodytes foetida* (alkaloid camptothecin), *Catharanthus roseus* (terpenoid indole alkaloids vincristine and vinblastine), *Taxus wallichiana* (diterpenoid taxol)

goes on to define its medicinal, nutritional or industrial/aromatic value. Recently, horticulture crops have also gained focus due to their direct implication in functional foods and possessing health ingredients (nutraceuticals) and there are several existing opportunities for the industry if it endeavours to fill in the existing gaps in the development of biofortified foods [3].

Bioprospecting for novel molecules from plant resources and novel bioactivities for previously known phytomolecules is the major activity towards development of plant-derived drugs. In recent years this activity has intensified with many labs across the globe participating in it. Plant sourcing for health services to the human life can be exemplified by taking appropriate therapeutic categories. For example, as shown in Table 1 some such categories could be providing the service in health sector involving major ailments and diseases that humans suffer. These include the billion dollar categories like nervine tonics, anti-obesity, anti-diabetes, anti-cancer, etc. Several plant species have been identified for serving many of these therapeutic categories.

The Path Through Pathways—Bioprospecting Plant Bioactives for Health

Indeed the dynamic plant metabolome provides an opportunity to tread a bioprospection discovery path through the various secondary metabolite biosynthetic pathways [4]. While plant leaf, stem and root extracts have been widely evaluated for bioactive compounds, screening of plant flowers and seed has not been extensive [5]. In a typical study, the seeds of some coprophilous plants have been observed to possess antimicrobial activity [6, 7]. In another facet of the therapeutic utility of plants, novel biosensors could be designed from higher plants, which have the capability of detecting environmental hazards and bioactive molecules through their distinct responses [8]. Table 2 lists some examples of plant-sourced bioactive compounds.

It is established that the biosynthetic pathway for a particular secondary metabolite may exist in many different plant species. Such a scenario is best exemplified by the case of camptothecin. This highly potent anti-cancer phytomolecule is usually isolated from *Camptotheca acuminata* (Nyssaceae) but is not exclusive to this plant species. It has also been reported to be produced substantially well in *Ophiorrhiza pumila* (Rubiaceae) and *Mappia foetida*. It is a modified monoterpene indole alkaloid also produced by *Nothapodytes foetida*, *Pyrenacantha klaineana*, *Merrilliodendron megacarpum* (Icacinaceae), *Ervatamia heyneana* (Apocynaceae) and *Mostuea brunonis* (Gelsemiaceae), species belonging to unrelated orders of angiosperms [26].

This situation demands deeper insight through chemotaxonomic route and analyzing synteny in metabolomes of the species indicating functional genome phylogeny in a very different perspective allowing thinking of metabolic engineering breaking traditional taxonomic barriers. Nevertheless, specificity is also equally prevalent and observed. For instance, in these cases the phytomolecules are produced in a species-specific manner: for anticancer *Catharanthus roseus* alkaloids (vincristine and vinblastine), the narcotic analgesic from *Papaver somniferum* (morphine) and the antimalarial from *Artemisia annua* (artemisinin). This situation raises the need to go for metabolome prospecting for pathway steps rather than the end metabolites to plan for engineering pathway branches or extension steps from other species in case designer crops or plant bioreactors are targeted. Further, the path followed by the metabolic flux may tread different paths in the same

Table 2 Case examples of plant-derived bioactive compounds through bioprospection

S. No.	Plant source (plant part)	Bioactivity	Active constituents	Reference
1	*Oenothera biennis* (roots)	Antibacterial	Oenostacin (3,5-dihydroxy-4-pent-4′-enoyl-1′-oxymethylbenzoic acid)	US patent nos. 6, 365, 197 and 6, 451, 356; Shukla et al. [9]
2	*Bixa orellana* (seeds)	Antibacterial	Bixin, methyl gallate, monomethylellagic acid	Shukla et al. [10]
3	Cruciferous vegetables (like cabbage and cauliflower)	Anti-carcinogenic	Indole-3-carbinol (I3C)	Baldwin and LeBlanc [11]; Wattenberg [12]
4	*A. annua* (leaves)	Antimalarial	Artemisinin	Qinghaosu Antimalarial Coordinating Group [13]
5	*Taxus brevifolia* (bark)	Anticancer	Taxol	Wani et al. [14]
6	*Moringa oleifera* (pods)	Bioenhancer	Niaziridin (nitrile glycoside)	US Patènt No. 6858588; Arya [15]
7	*C. roseus* (leaves)	Anticancer	Vincristine	Svoboda [16]
8	*C. roseus* (leaves)	Anticancer	Vinblastine	Noble et al. [17]; Johnson et al. [18]; Svoboda [19]; Svoboda et al. [20]
9	*C. acuminata* (bark)	Anticancer	Camptothecin	Wall et al. [21]
10	*Curcuma longa*	Anticancer	Curcumin	Kuttan et al. [22]
11	*Capsicum annuum* (placenta)	Antiangiogenic	Capsaicin	Min et al. [23]
12	*Rauwolfia serpentina* (roots)	Hypotensive	Reserpine	McQueen et al. [24]; Meier et al. [25]

organism also. Thus root and shoot profiles of secondary metabolites may be entirely different [27].

The microbiome adds another level of complexity in the functional flexibility of the metabolome. Both the plant-associated as well as the human gut microbiome have significant implications. The former may be responsible for the diversity of the plant secondary metabolite spectrum whereas the latter would differentiate the effect of same metabolite on different human individuals. Recently, a proof of concept of microbiome-metabolome analysis and delayed gluten exposure on celiac disease autoimmunity in genetically at-risk infants has been shown [28]. The human microbiome is at the interface of health and disease and both the microbiome and metagenome probably have major roles in defining health and disease, which makes their exploration a frontier area of research in human genetics [29]. Thus in a holistic way it can be said that the microbiome could be a key factor in defining the "*Prakriti*" or nature of both—the plant as well as the human. Thinking of human genome in isolation for disease prevention or control strategy perhaps would not work unless the microflora of the gut are taken into consideration as the integrated genomic capabilities and need. A right balance of the microbiome diversity associated with human health would also need attention for a health service by any agents including plant-derived phytoceuticals or nutraceuticals.

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