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Review Paper

ENVIRONMENTAL IMPACT OF SECONDARY METABOLISM ON MEDICINAL PLANTS

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Abstract

Medicinal plants constitute main resource base of almost all the traditional healthcare systems. Most of the herbal drugs produced currently in majority of the developing countries lack proper quality specification and standards. Herbal drugs used in traditional medicine may contain a single herb or combinations of several different herbs believed to have complementary and/or synergistic effects. Both the raw drugs and the finished herbal products manufactured contain complex mixtures of organic compounds, such as fatty acids, sterols, alkaloids, flavonoids, polyphenols, glycosides, saponins, tannins, terpenes etc. The quality of the finished product is based on the quality of the raw materials, which is again depends on mineral composition of soil, geographical area etc. As many as 35% of the medicinal plants used in Indian systems of medicine are highly cross pollinated which indicate the existence of a wide range of genetic variability in the populations of these medicinal plant species which in turn reflected in the variations in the composition of secondary metabolites. Ecological and edaphic as well as seasonal variations also cause changes in the chemical composition of medicinal plants. These facts have to be considered while developing quality parameters standards of medicinal plants and their finished products.

Key words: Medicinal Plants; Organic Compounds; Secondary Metabolite; Biosynthesis.

Abbreviations: Secondary Metabolites (SMs); Coenzyme A (CoA); Adenosine Diphosphate (ADP); Adenosine Triphosphate (ATP); Nicotinamide Adenine Dinucleotide Phosphate (NADP); Acetyl Coenzyme A (Acetyl-CoA)

Purpose of the study: An illustrated review of factors that influence secondary metabolism of plants and their impacts on therapeutic efficacy.

Findings: Traditional plants are used from ancient time for various human well-being, both as life-saving and lifestyle drugs. A careful observation may explore facts behind therapeutic efficacy of these plants.

Materials and Methods: A comprehensive literature review, consulting books, technical newsletters, herb magazines, journals, and many other sources. Health professionals like qualified doctors, herbal specialists, folk healers, alternative medicine specialists given their valuable suggestions.

Research limitations: The limitation lies with the unlimited information about traditional medicines. Validity of those are very hard to prove. Only data obtained from books, newsletters, national and international research-based articles are given here along with surrounding facts mostly visible. A few many plant medicine books consulted earlier but article has fewer scope to add from them.

Practical Implication: the article is based on plant medicine which is a specialized topic. Students, researchers and professionals may acquire much from this article.

Introduction

While in food plants our main interest is the carbohydrate/ sugars, proteins, fats and other vitamins, in medicinal plants we look for therapeutically useful chemicals which are generally termed as secondary metabolites which are not that essential for the normal growth and development of the plants/organisms. Plants synthesize these compounds to protect themselves i.e. to adjust, adapt or defend/ offend, from the hostile organisms or diseases or the environment. SMs that are useful in medicine are mostly polyphenols, alkaloids, glycosides, terpenes, flavonoids, coumarins, tannins etc. The production of secondary metabolites although controlled by genes but their specific expression is greatly influenced by various factors including biotic and abiotic environments such as climate and edaphic factors or other associated living organisms. During the course of evolution plants have evolved various physical and chemical mechanisms to protect themselves from the vagaries of nature (drought, heat, rain, flood, etc.) and also to defend or offend the predators or to protect from predators and pathogens. The most successful adaptation of plants while developing various physiological mechanisms is through the production of a variety of phytochemicals by which they were able to face both biotic and abiotic stresses and threats. In this process of defense/ offence from abiotic stress or the invading diseases causing organisms or the predators (animals, birds, insects and herbivorous animals), the plant synthesize a variety of chemical compounds. Apparently, plants produce many antioxidants for protecting themselves from the oxidative stress. These compounds are in general stored in the leaves or other parts such as, bark, hardwood, fruits, etc., so that the predators or the disease-causing organisms can be either knocked down or paralyzed or even get killed. In many cases, the production of the secondary metabolites in plant also depends on the association of other living organisms, more particularly, the plant or soil microbes. Such differential expressions of therapeutically active principles in plant on account of the above said factors appears to have known and well understood by the

ancient scholars, when they gave specific instructions in the procurement of medicinal plants.

Biosynthesis

The pathways of biosynthesis are responsible for the occurrence of both primary and secondary metabolites illustrated in figure 1. Biosynthetic reactions are energy consuming, fueled by the energy released by glycolysis of carbohydrates and through the citric acid cycle. Oxidation of glucose, fatty acids and amino acids results in ATP formation, which is a high-energy molecule formed by catabolism of primary compounds. ATP is recycled in fuel anabolic reactions involving intermediate molecules on the pathways. Whereas, catabolism involves oxidation of starting molecules, biosynthesis or anabolism involves reduction reaction. Hence, the need of reducing agent or hydrogen donor, which is usually the NADP. These catalysts are known as coenzymes and the most widely occurring is CoA made up of ADP and pantetheine phosphate. The most common pathways taken for biosynthesis are performed through the pentose for glycosides, polysaccharides; shikimic acid for phenols, tannins, aromatic alkaloids; acetate-malonate for phenols and alkaloids and mevalonic acid for terpenes, steroids and alkaloids. As showed in the Fig. 1, the scheme outlines how metabolites from the process of photosynthesis, glycolysis and Krebs cycle are tapped off from energy-generating process to provide biosynthetic intermediates. By far, the important building blocks employed in the biosynthesis of secondary metabolites are derived from Acetyl-CoA, shikimic acid, mevalonic acid and 1-deoxylulose 5-phosphate [1-7].

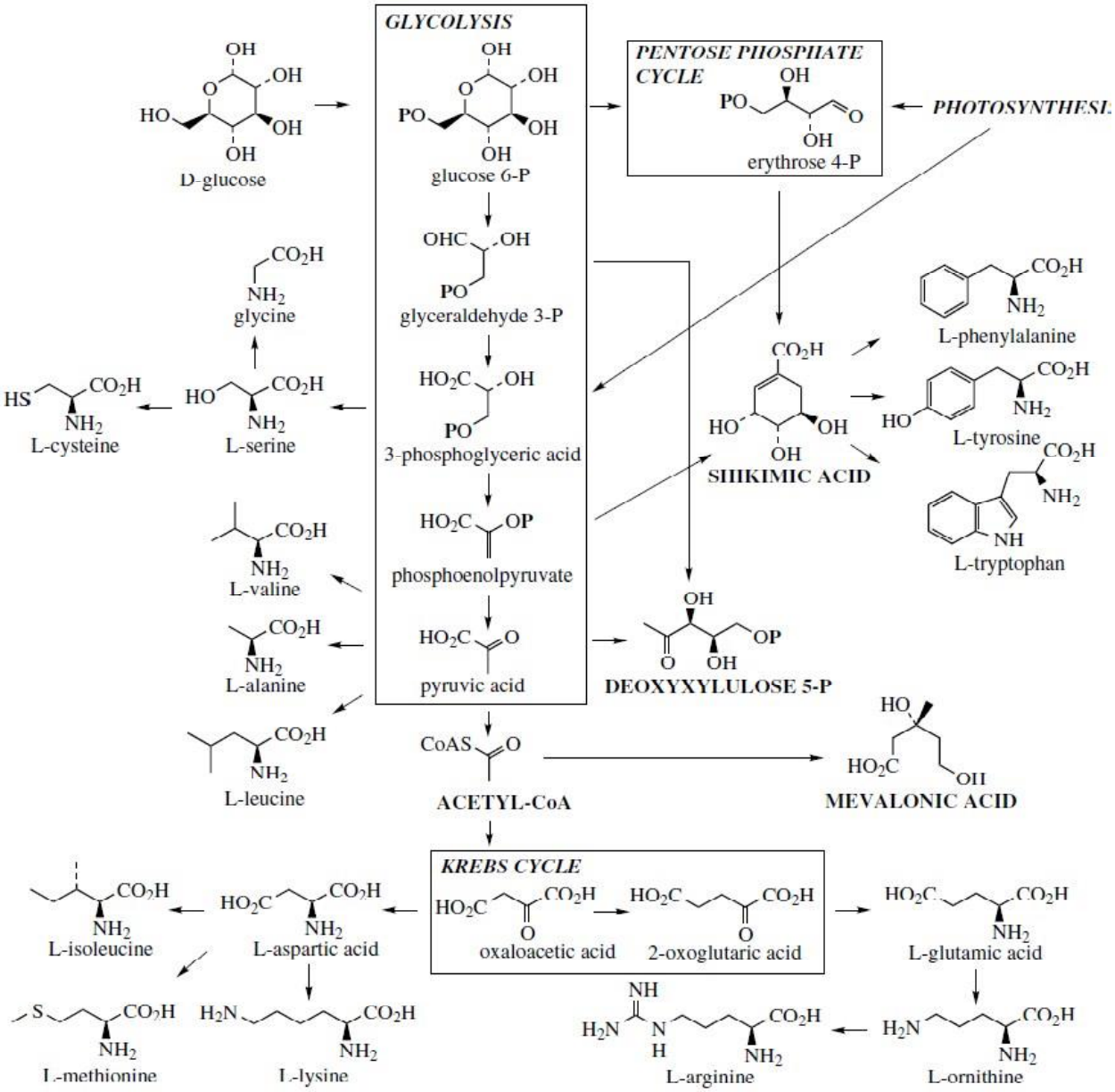

Figure 1. Biosynthesis scheme of plants secondary metabolites [8].

Expression of Secondary Metabolites

The presence of or absence of certain secondary metabolites in medicinal plants are influenced by a variety of factors, which include climate/ season, edaphic conditions or the association of other plants and other living organisms [9]. Another factor that influenced the production of secondary metabolites in plants are the inter relationship between plants and the insect flora. It is now generally accepted that the flora and the insect flora in a tropical ecosystem have been co-evolving and co-adapting. Many of the medicinal plants are cross-pollinated and they need the help of pollinators. In an open area the wind could do the function, but in a canopied forest many of the shrubs and herbs growing under the big trees cannot get wind to pollinate. These plants are thus heavily depending upon the insects or even the birds to pollinate them. To attract the insects or birds the plants develop pleasant aroma (essential oils) and provide honey and pollen as food to these pollinators. Many flowers contain honey or pollen, which are

the normal food of many insects and birds [10, 11]. The insects like bees and butterflies visit flowers after flowers, and take honey or pollen or both. During this process they also carry pollen on their body part, which then help in pollinating while visiting other plants. Many flowers have structurally evolved flower parts to affect such pollinations by insects. These insects also multiply on plants. They lay millions of eggs and the larvae that emerge from these eggs then feed on leaves of the plants, sometimes destroying the plants altogether by over feeding. During the course of evolution, the plants began to synthesize certain toxic substance so that a good percentage of the feeding larvae could be killed [12, 13, 14]. The insect on the other hand began to develop resistance so that many of the larvae could survive. The plants on the other hand again counteracted. It synthesizing more and more toxic compounds. This was something like the love and hate relationship between plants and the insects, which during the course of millions of years of evolutions have resulted in the synthesis of innumerable chemical compounds, mostly the secondary metabolites in plants as well as in insects [15,16]. The variability in living organisms is indeed the insurance for survival. The evolutionary origin of cross breeding was indeed a nature's device for reshuffling of genes so that new variants could be produced. Similarly, the abiotic conditions also exerted certain influence in the plants and the plants responded by developing various chemicals [17]. In extreme drought conditions the desert exerts a kind of stress on the plants and the plants evolve by synthesizing chemicals that would help them to protect from stress induced by the desert conditions. An excellent example for this is the plant *Commiphora wightii*; an important medicinal plant used extensively as complimentary medicine named 'Guggul'. The medicinal part of the plant is the gum exudates from the stem bark of living plants. This gum is traditionally collected from the desert regions of Rajasthan, Gujarat and even Afghanistan. To everyone's surprise the chemical data of this gum revealed that it does not contain most of the active compounds. A logical explanation may be that this plant growing in a warm humid tropical forest region. It has no desert like conditions and therefore there is no question of any drought induced stress. The same plant when growing in desert has to confront drought induced stress and the plant synthesizes the stress beating chemicals. There are many similar cases that demonstrate that certain specific climatic conditions and edaphic situations are extremely important in the production of therapeutically desirable medicinal compounds. Sandalwood is another classical example. The specific aroma of sandalwood is due to the presence of certain essential oil chemicals, mostly monoterpenes and sesquiterpenes. The production of the specific aroma chemicals is fully expressed only in those sandalwood trees that grow in certain forest regions of Karnataka. The sandalwood growing in other places in India or elsewhere in the world do not have the same kind of aroma with the corresponding chemical constituents [18, 19, 20].

Importance of Secondary Metabolites

Secondary metabolites, which are a characteristic feature of plants, are especially important and can protect plants against a wide variety of microorganisms (viruses, bacteria, fungi) and herbivores (arthropods, vertebrates). As is the situation with all defense systems of plants and animals, a few specialized pathogens have evolved in plants and have overcome the chemical defense barrier. Secondary metabolites, including antibiotics, are produced in nature and serve survival functions for the organisms producing them. Secondary metabolites serve:

(i) As competitive weapons used against other bacteria, fungi, amoebae, plants, insects, and large animals;

(ii) As metal transporting agents;
(iii) As agents of symbiosis between microbes and plants, nematodes, insects, and higher animals;
(iv) As sexual hormones; and
(v) As differentiation effectors.

Although antibiotics are not obligatory for sporulation, some secondary metabolites (including antibiotics) stimulate spore formation and inhibit or stimulate germination. Formation of secondary metabolites and spores are regulated by similar factors. Thus, the secondary metabolite can:

(i) Slow down germination of spores until a less competitive environment and more favorable conditions for growth exist;
(ii) Protect the dormant or initiated spore from consumption by amoebae; or
(iii) Cleanse the immediate environment of competing microorganisms during germination [21, 22, 23, 24].

Environmental Stress and Secondary Metabolites in Plants

Environmental factors significantly affect plant growth and biosynthesis of SMs. Plant growth and productivity is negatively affected by temperature extremes, salinity, and drought stress. Plant SMs are compounds that play an essential part in the interaction of plants with abiotic stresses [25]. In addition, plant growth and development are also largely mediated by the endogenous levels of these SMs. A wide range of SMs are produced from primary metabolites such as amino acids, lipids, and carbohydrates in higher plants. Particular colors, tastes, and odors of plants are associated with SMs. Plant SMs also serve as essential sources of industrially important chemicals, flavors, food additives, and pharmaceuticals [26]. Plants accumulate such compounds in response to different signaling molecules. SM production is influenced by various environmental stresses. Environmental factors determine the synthesis and subsequent accumulation of SM. Alteration in any one factor triggers perturbations in the biosynthesis of plant SMs [27].

Differential Responses of Plants to Biotic Stress

Plants contribute a lot to this universe but they have to face many stresses of biotic or abiotic nature. Biotic stress is a severe environmental constraint to the plant's productivity. Biotic stress induces loss in crop yield probably more than the cumulative losses from all other factors. In any stress, the type and duration are critical for plant growth [28]. Plants use various defensive strategies to tolerate these adverse factors. Of the various defensive mechanisms, one is the production of reactive oxygen species. These defensive mechanisms against biotic stress are generated as a result of the continuous interaction between plant and pathogen [29]. Plants' responses to biotic stress are not only the alteration in anatomical features, such as formation of a waxy cuticle, trichrome, setae, and spines, but also the production of various secondary metabolites. Such types of plant responses have been observed against bacteria, fungi, and pests. These secondary metabolites trigger different plant defense mechanisms in the form of ascorbic acid, antioxidative enzymes (peroxidase, polyphenol oxidase, lipoxygenases), salicylic acid, jasmonic acid, and Ca2+ against biotic stress and also act as toxins (terpenes, alkaloids, and phenolic compounds) against plant pathogens [30].

Engineering of Biomass Accumulation and Secondary Metabolite Production

Plants are the source of valuable secondary metabolites that are commonly used in pharmaceutical, food, agricultural, cosmetic, and textile industries [31]. Plant cell and tissue culture technologies can be established routinely under sterile conditions from explants, such as plant leaves, stems, roots, and meristems for both the ways for multiplication and extraction of secondary metabolites. In vitro production of secondary metabolite in plant cell suspension cultures has been reported from various medicinal plants, and bioreactors are the key step for their commercial production. Based on this lime light, the present review is aimed to cover phytotherapeutic application and recent advancement for the production of some important plant pharmaceuticals [32]. The increasing commercial importance of secondary metabolites has resulted in a great interest in research focusing on secondary metabolism and finding alternative ways for secondary metabolite production. Plant cell and tissue cultures are branches of plant biotechnology and they have been introduced as alternative ways for the production of valuable secondary metabolites. Plant technology provides a continuous and reliable source for pharmaceutical phytochemicals and can easily be scaled up [33]. Therefore, plant cell and tissue cultures have a great potential to be used as an alternative to traditional agriculture for the industrial production of secondary metabolites [34, 35].

Conclusion

SMs are the useful natural products that are synthesized through secondary metabolism in the plants. The production of some secondary metabolites is linked to the induction of morphological differentiation and it appears that as the cells undergo morphological differentiation and maturation during plant growth. It is observed that in-Vitro production of secondary metabolites is much higher from differentiated tissues when compared to non-differentiated or less –differentiated tissues. There are lots of advantages of these metabolites like there is recovery of the products will be easy and plant cultures are particularly useful in case of plants which are difficult or expensive and selection of cell lines for high yield of secondary metabolites will be easy. Many other examples could be presented with plant metabolic engineering as this research area is developing actively. Metabolic engineering is probably a large step forward but playing on the genes will not solve all the problems that have prevented the development of commercial success in the field of plant secondary metabolites. And Advances in plant cell cultures could provide new means for the cost-effective, commercial production of even rare or exotic plants, their cells, and the chemicals that they will produce. Knowledge of the biosynthetic pathways of desired compounds in plants as well as of cultures is often still rudimentary, and strategies are consequently needed to develop information based on a cellular and molecular level. Because of the complex and incompletely understood nature of plant cells in-vitro cultures, case-by-case studies have been used to explain the problems occurring in the production of secondary metabolites from cultured plant cells. Advance research has succeeded in producing a wide range of valuable secondary phytochemical in unorganized callus or suspension cultures till to date; in other cases, production requires more differentiated micro plant or organ cultures.

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Compliance with Ethical Standards

•Ethics approval and consent to participate
Animal and Human experiment: N/A
Human Data Submission Approval: N/A
•Consent for publication
Consent to publish Individual Person's data: N/A
•Availability of data and materials
Data sharing: Please contact author for data requests
•Competing interests
The authors declare that they have no competing interests
•Funding
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The individual contributions of authors: N/A

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