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Botanical Pesticides: Current Challenges and Reverse Pharmacological Approach for Future Discoveries

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Introduction

In ancient culture and in different parts of world, there exist empirical knowledge of the use of plants for pest control for thousands of years (approx. 1500 BC), for example rotenone in east Asia and south America, neem in India, sabadilla in central and south America, and pyrethrin in Persia (Iran). Subsequently, botanical insecticides were introduced in prominent continents like Europe and United states [1]. Botanicals (phytochemicals) are basically secondary metabolites that serve as means of defense mechanism of the plants to withstand the continuous selection pressure from herbivore predators and other environmental factors. Many groups of phytochemicals such as steroids, alkaloids, terpenoids, phenolics and essential oils from more than 2000 plant species have been reported previously for their insecticidal activities. Applications of phytochemicals in mosquito control were in use since 1920, but the discovery of synthetic insecticides such as DDT in 1939 sidetracked the application of phytochemicals in different segments. Synthetic insecticides spread easily and rapidly because it won space on market as products being effective, cheaper, long lasting and easily available. After facing problems due to injudicious and over application of synthetic insecticides in nature, refocus on phytochemicals that are easily biodegradable and have no ill effects on non-target organisms was appreciated. From 1990s, there is renewed interest for use of botanical pesticides due to concerns raised about the rampant supply of synthetic insecticides and its irreversible impact on health and environment; its presence in food web is quite worrying matter for health professionals. At present, phytochemicals make up to 1% of world's pesticide market [2].

Current Research and Commercialization Challenges

In a quest of finding solutions for ubiquitous harmful insects through botanicals, there has been considerable research happening in the world. However, very few research projects translate in to distinct product launches. Everybody wants to have quick results for saving cost, time and energy. Hence, most of the academic research is perhaps incomplete because of its design having short term goals. As a result, the outcome is effected by poorly conducted study, inadequate data, poor analytical work, invalidated data, superficial experimentation having exclusive objective to have a publication. Therefore, funding authorities should give serious thought as to how the research reaches to the end point through systematic research and team efforts of different stake holders. Plant based research in India is no longer piece of cake for anybody in view of Biodiversity legislation, 2002. Anybody plans to work on plants, one has to get permission from State Biodiversity Board (SBB). SBB will hold meetings with local management committees and experts from the field of plant taxonomy, social forestry, zoology, geology, ornithology, etc and then permission is granted. Then actual collection, processing and screening samples for proposed bioactivity is initiated. Once bioactivity is discovered in a plant, then the commercialization of that plant based product remains to be great challenge. First and foremost priority should be generating proof of concept data by collecting same species from different districts covering different phytogeographical locations, collection in different seasons, collecting species in different stages, collection of different plant parts of same species, processing of the same up to extraction and lastly systematic biological evaluations on concerned pest of interest. Side by side, one also have to rule out the possible external causes of bioactivity (e.g., whether or not the efficacy is due to residual pesticides that may have been sprayed on crops in agricultural land).

Consumption of herbal/Ayurveda medicine is widespread and increasing. The chief source of raw material is harvesting herbs from the wild which is causing loss of genetic diversity and damage to plant habitat. Therefore, domestic cultivation is a viable alternative that offers opportunity to overcome challenges of inconsistency in plant materials and extracts due to factors like wrong identification, phenotypic and genetic variability, extract variability and unstable nature for longer timespan, toxic components and contaminants. For commercialization of any plant based product, raw material sourcing is a real challenge. There are challenges for cultivation and propagation of any wild species. If propagation is by seeds, then it has go through germination, domestication studies, developing package and practices for cultivation, determining pesticidal and manure requirements, re-establishing the bioactivity profile of the plants produced from ex-situ cultivation, addressing factors like change in climate, soil, rainfall, temperature where cultivation is taking place, mobilization of hundreds of hectares of land, testing soil for deciding manure/minerals etc. requirements, assessment of impact of the cultivation on the people residing around those villages, assessment of impact of large scale cultivation on environment vis-à-vis pollen allergies, species (under cultivation) competing with native species, any adverse effect on soil fertility if species under cultivation is having affinity with water and also crop rotation studies. Cultivation of the bioactive plant species will depends on habit of the plant, habitat, size of the seeds, dormancy pattern, seasonality, annual/perennial, secondary metabolites generation, climate, geology, rainfall, endemism, status of the species (rare, threatened, endangered, critically endangered), rules & regulations for that species germplasm, seed coat pattern, etc. Alternative route can be through controlled environments which will solve problems of cultivation. This can also manipulate phenotypic variation in bioactive compounds and toxins. Conventional plant-breeding programme may improve both agronomic and medicinal traits. There has been significant progress in biotechnological methods like tissue culture and genetic engineering in altering biosynthesis of target molecules.

Reverse Pharmacology: A Way to Botanical Pesticide Discovery

As per Katiyar et al. [3], total number of higher plants species (comprising angiosperms and gymnosperms) is approximately 250,000, out of them only 6% have been screened for biological activity. Initial listing of the candidate species for screening of biological activity is a major task of specific importance in itself. For the purpose, Fabricant and Farnsworth [4], proposed following approaches.

First is random approach in which the plants collected randomly and screened them irrespective of their contents or reports in literature. National Cancer Institute (NCI) of National Institute of Health, USA, thoroughly studied about 35,000 plant species for anticancerous segment investing over two decades (1960-1980), discovered two molecules viz., paclitaxel and camptothecin.

Second is traditional system of medicine approach; countries like India and China have a rich heritage of well-documented traditional system of medicine. Discovery of artemisinin from *Artemesia alba* for malaria; guggulsterones from *Commiphora mukul* for hyperlipidemia; boswellic acids from *Boswellia serrata* for anti-inflammatory properties; bacosides from *Bacopa monnieri* as nootropic and memory enhancement; reserpine from *Rauwolfia serpentina* was based on the leads from these codified systems of medicine prevailing in China and India.

Third is ethnopharmacology approach; this essentially depends on empirical experiences related to the use of botanical drugs for the discovery of NCEs having target specific activity. Whole process comprises observation, description, and in-vitro or in-vivo experimental investigation of indigenous formulations, and is based on chemistry, botany, biochemistry, pharmacology and other different disciplines like archaeology, anthropology, history and linguistics. This approach based on ethnomedicinal usage history that has seen some successes like *Andrographis paniculata* being used for dysentery in ethnomedicine and the compounds responsible for the activity were isolated as andrographolide; Morphine from *Papaver somniferum;* Berberine from *Berberis aristata* and *Picroside* from *Picrorrhiza kurroa* are some examples of this approach. This approach seems to be appropriate because, biological, ecological and cultural diversity of any nation leads to generation of empirical and scientific knowledge, the first has its origin in ancient times with practices of observation of the nature and experimentation through trial and error, and inheritance transmitted from generation to generation through test and stories. Botanists have been interested in reviewing corroborated and enriched ethnoflora stating biological significance and the search for new pesticidal phytocompounds useful in protecting and preserving food. Ethnobotany is considered as source for research of phytopesticides of interest to agricultural as well as protection from fatal diseases caused by mosquitoes. Hence, ethnobotanical studies are now recognized to be most viable methods of identifying new medicinal plants. In 2010, Kshirsagar et al. [5], discovered antioxidant and anti-inflammatory compounds from tubers of *Eulophiao chreata*, namely; 9,10-Dihydro-2,5-Dimethoxyphenanthrene-1,7-diol and 5,7-Dimethoxyphenanthrene- 2,6-diol. Since time immortal, the tubers have been used by Pawra tribe of Satpuda mountain ranges of Maharashtra for rejuvenating, aphrodisiac and anti-inflammatory properties.

However, in India, ethnopharmacological approach for finding biopesticidal botanicals has been considerably underexplored. In 1991, Jain [6] published dictionary of Indian Folk Medicine and Ethnobotany based on compilation of research of preceding 30 years. The dictionary reports just 4 plants as biopesticides out of 2532 species which clearly indicates that this field remains significantly unexplored. In last two decades only few research papers throw some light on this topic. For example, Phani Kumar and AlkaChaturvedi [7] tell about 2 plants for insecticidal property. Bhardwaj et al. [8], deals with various plants are being used as ethnomedicines against insects and worms in Aravalli hill range of India. Senthilkumar et al. [9] deals with insecticidal properties of certain flora based on ethnobotanical records against Teak defoliator. Anjali Mathur and Hema Joshi [10] mention about 8 plants being insecticidal. Considering the gap in ethnobotanical knowledge documentation and its systematic biopesticidal exploration by using modern techniques and sophisticated instruments, the efforts should be made to bridge the gap by initiating aggressive studies, since, India harbors around 400 different tribes amounting to 7.5% population of whole country.

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