GUEST EDITORIAL

NATURAL PRODUCTS – A CONTINUING SOURCE FOR NEW DRUGS

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The 2015 Nobel Prize in Medicine has been awarded to William Campbell and Satoshi Omura for their discovery of microbial natural product avermectins and Youyou Tu for the discovery of plant natural product artemisinin. These natural products not only revolutionized the treatment of devastating parasite diseases but also brought great pride and optimism to the community dealing with natural products worldwide.

The term "natural products" is often used synonymously with secondary metabolites. They are chemical substances produced by living organisms found in nature. Unlike primary metabolites, secondary metabolites are not directly involved in growth, development and reproduction of an organism. Further, their distribution is restricted to a particular species or family. However, secondary metabolites aid organisms in which they are found, in order to carry out important functions that include protection, defense, sexual attraction, social communication and identification. Most importantly, they possess interesting biological or pharmacological properties that could be exploited in the process of drug discovery.

Natural products can be obtained from different sources. The plant kingdom is a rich source of natural products. Not only the plant kingdom, but also microorganisms such as bacteria and fungi, coral, sponges and fish of the marine world, animals and also venoms and toxins from snakes, spiders, scorpions and insects possess myriad of interesting natural products.

The very first natural product to be isolated was the analgesic and sleep-inducing agent from opium produced by cut seed pods of the poppy, Papaver somniferum in the beginning of the 19th century by a pharmacist's apprentice named Friedrich Sertürner. He named this morphium (morphine) after the Greek god of dreams, Morpheus as it has a tendency to cause sleep. Since the discovery of morphine, it has held its stature as one of the most potent analgesics to date.

Serturner's work proved that plants contain active substances that, in isolation, carry out the therapeutic properties of the plant. The discovery of morphine also led to the emergence of natural products chemistry as an independent discipline. Further, this triggered the examination of other medicinal plants and natural sources, and through-out the 19th and 20th centuries many natural products were isolated from their natural sources as therapeutic agents.

In natural products related drug discovery and development, initially crude extracts are obtained from medicinal plants. Crude extracts are subjected to bioassays and in the presence of activity, the extract is fractionated and active compounds are isolated and identified. Every step of fractionation and isolation is usually guided by bioassays, or else crude extracts are fractionated and compounds are isolated and identified, which are then subjected for bioassays. 'HIT' compounds that results from initial screening work are subjected to further screening and suitable lead compounds are selected for the drug development process. Lead compound is a compound with some interesting biological or pharmacological activity, but not yet good enough to be the drug itself. It will undergo the following steps before a new drug emerges from it.

- Synthesize analogs of the lead compound
- Carry out structure-activity-relationship studies to identify the "pharmacophore"
- Optimize the structure of the lead compound (pharmacophore) to improve interactions with the target
- Determine toxicity and efficacy in animal models
- Determine pharmacodynamics and pharmacokinetics of the compound
- Patent the drug
- Continue to study drug metabolism and toxicity
- Design a manufacturing process
- Carry out clinical trials
- Market the drug

The process can be slow, inefficient, labor intensive and very expensive. There is also no guarantee that a lead compound would be chemically workable, patentable or even result in a new drug. Further, difficulty in isolating active compounds from extracts, lack of reproducible results, slow growth and sparsely distribution of species from which natural products are obtained, long resupply time for active extracts and problems with large scale supply if a drug emerges from natural sources were challenges that declined interest in natural products related drug discovery and development towards the end of the 20th century.

However, today there is renewed interest as research in to natural products drug discovery and development is coupled with modern methods involving novel technologies. It has also become a multidisciplinary science by embracing diverse fields. Further advances in smart screening methods, robotic separation with structural analysis, metabolic engineering, synthetic biology, computational chemistry etc. coupled with untapped biological resources will enable new drugs to come to clinical trials and the market place more rapidly and with a higher rate of success.

Natural products have been an extremely productive source for new drugs in the past and will continue to do so in years to come.