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Review Article

Natural products drug discovery research in India: Status and appraisal

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Discovery of a new drug is time consuming and laborious process. Natural products have long been a thriving source for the discovery of new drugs due to their chemical diversity and ability to act on various biological targets. The phytochemical exploration of indigeneous flora has contributed to some extent in this race for the discovery of new drugs. The traditional Indian systems of medicine has been a part of our lifestyle since ages and the classical texts like Ayurveda and Charak Samhita have served as materia medica for this purpose. This review focuses on the contributions made from India in the drug discovery and development process and provides future directions in the area.

Keywords : Anti-diabetic, Anti-malaria, Anti-obestiy, Cardio-protection, Natural products

Natural products remain a prolific source for the discovery of new drugs and drug leads even from Vedic period. Recent data suggests that 80% drug molecules are natural products or natural compound inspired[1]. Studies on sources of new drugs from 1981 to 2007 reveal that almost half of the drugs approved since 1994 are based on natural products[2]. Indian natural products, particularly those from traditional medicinal plants which are reported in the classic texts like Ayurveda and Charak Samhita, have contributed towards this 'boom' in drug discovery. The rich biodiversity of India has remained untouched as far as discovery of new chemical entities is concerned. The drug discovery process from plants is, however, a laborious and time consuming process (Fig. 1). This review focuses on the role of Indian medicinal plants in the global drug discovery process mainly in the disease areas like cardiovascular, metabolic, inflammatory, viral, parasitic and cancer.

The conventional rediscovery process aims to identify a single, pure active constituent from an active extract and a method to estimate it in the crude drug. The classical examples of drug discovery like morphine, quinine, digoxin, etc which replaced the extracts of their respective plants were mostly responsible for harbouring the idea that a single active ingredient must have been responsible for the bioactivity. The drawback of this ideology is that it does not look into the synergy or antagonism characteristics present in the mixture. Apart from this some constituents may also possess other diverse activities. This factor is corroborated by several examples reported in literature where the ascribed pharmacological activity of the extracts could not be matched with that of the isolated pure compounds. Most of the newer work on medicinal plants is mostly the rediscovery of effects known for a long period of time at cellular and molecular levels. The uncertainty of earlier studies is obvious in case of biological activity because of the lack of standardization techniques or instances where even if present were in a primitive state.

The traditional Indian system of medicine has a very long term history of usage in a number of diseases and disorders, but lacks recorded safety and efficacy data. However, the main cause for their scientific neglect is due to multi-constituent mainstay and the mechanism of action being unclear. But recently, it has been suggested that drug discovery should not always be limited to discovery of a single molecule and the current belief 'one disease-one drug' approach may be untenable in the future and that rationally designed polyherbal formulations could also be investigated as an alternative in multi-target therapeutics and prophylaxis[3]. Development of standardized, safe and effective herbal formulations with proven scientific evidence can also provide an economical alternative in several disease areas. Still some pro's and con's need attention for improvement of traditional Indian medicines (Fig 2).

Other factor that draws attention is that the phytomedicines used in the Western countries are indicated for a particular disease or condition. This is opposite to the Indian system of medicine where the formulations are indicated for a myriad of conditions.

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Keeping this in view, the present review reveals the possibility to recast and develop the Ayurvedic/Indian traditional system of medicines in this manner with disease specific perspective.

Drug discovery from plants and traditional medicines in India

Recently, a rejuvenation effort for drug discovery process from natural products has been undertaken by the Council of Scientific and Industrial Research (CSIR), Govt. of India in the shape of a coordinated programme involving 19 CSIR laboratories under its hub and other R&D institutes in the field of traditional medicines along with a few academic departments of the universities in India. This initiative started in 1996 aimed at discovering new bioactive molecules from natural sources like plants, fungi, microbes, insects, etc. Amongst the institutes CSIR labs, Central Drug Research Institute (CDRI), Lucknow, and Regional Research Laboratory (RRL), Jammu (Indian Institute of Integrative Medicine (IIIM), Jammu) have taken the lead in drug discovery endeavours.

Golden Triangle Partnership (GTP) has been introduced recently as a combined effort by three major Govt. of India institutes *viz.* Department of Ayush, ICMR and CSIR for the validation of traditional Ayurvedic drugs and development of new drugs. The main objective of this scheme is to bring safe, effective and standard Ayurvedic formulations along with Siddha, Unani and homoeopathic system of medicine, besides developing new drugs of national and global importance. A recent reportsuggests that around 38 Ayurvedic formulations have been attempted for 8 disease conditions and out of these 20 formulations have been submitted to CSIR for pre-clinical studies under the GTP scheme[4].

Unfortunately, there are few industrial players, when it comes to drug discovery from plants. Most of them restricting their focus on herbal formulations. The enormous cost involved in isolation of pure compounds from plants is perhaps the prohibitive factor. Therefore, most of the natural products research for drug discovery perspective remains as an academic exercise rather than a full fledged program. India has been far behind the West when compared to the discovery of New Chemical Entities (NCEs) from plants. Most of the compounds of Indian plants are

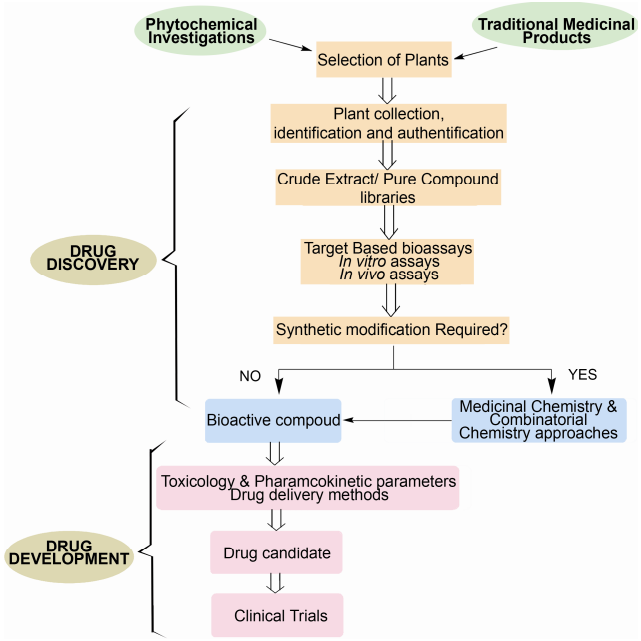

Fig 1— Process of drug discovery from plants

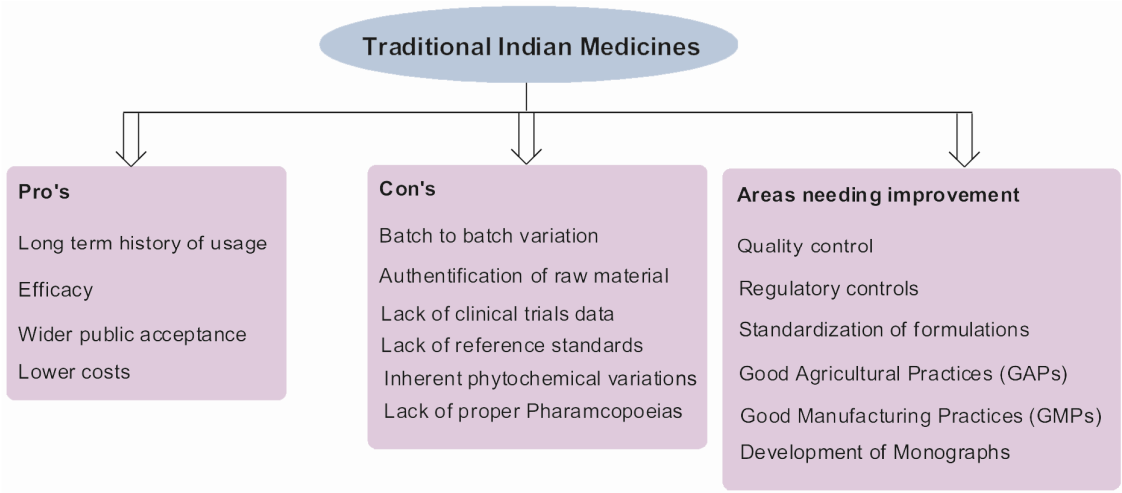

Fig 2—Dimensions of traditional Indian medicines

being isolated and screened abroad as is evident from the number of publications on Indian medicinal plants originating from the West.

Anti-inflammatory natural products

Inflammation is known to be one of the important causes responsible for many diseases. It has been associated with diseases like cancer and diabetes[5,6]. Pro-inflammatory cytokines (TNF-α and IL-1β) and NO are considered as the key mediators in inflammatory conditions like rheumatoid arthritis, sepsis etc. Thus, inhibition of pro-inflammatory cytokines and NO production are important targets for treatment of inflammatory disorders. Various Indian medicinal plants which are used in Ayurveda for the treatment of inflammatory conditions, have been found to contain chemical constituents that inhibit TNF-α and IL-1β production in various *in vitro* models[7]. Thus, these plants which have been used traditionally for inflammation have a potential to serve as sources of future drugs for treatment of various inflammatory diseases.

Withanolides from *Withania somnifera* are found to be active in arthritis and are potent inhibitors of angiogenesis, inflammation and oxidative stress. Inhibition of NFκB and NFκB-regulated gene expression is primarily responsible for their anti-arthritic action[8]. Salai guggal (*Boswellia serrata*) has been reported in many classical Indian texts for the treatment of several inflammatory diseases. This plant was investigated at IIIM, Jammu and has been reported to show anti-inflammatory and anti-arthritic activities[9]. The activity has been suggested to be due to presence of boswellic acids in this plant[10]. Later, Boswellic acid has been reported to inhibit of NFκB, COX-2 and 5-LOX[11]. Alkaloid, berberine found in the plant *Berberis aristata,* has been found to inhibit NFκB, COX-2, TNF-α, IL-1β, IL-6 responsible for the potent anti-inflammatory activity of this plant[12]. The most prominent example of anti-inflammatory natural product is curcumin from turmeric (*Curcuma longa*), a common household Indian spice. It has been reported in 1971 to be an effective anti-inflammatory agent at CDRI, Lucknow[13]. It shows a broad spectrum activity on inflammation by targeting NFκB, COX-2, 5-LOX, TNF-α, IL-1β, IL-6, IL-8, MMPs at a molecular level[14]. Another well studied natural product from Indian plants is guggulsterone from *Commiphora mukul* (guggul) which is a potent inhibitor NFκB, COX-2 and MMP-9[15]. Other known examples include nimbidin from neem (*Azadirachta indica*) and embelin a constituent of vidang (*Embelia ribes*) which has been reported to show potent anti-inflammatory activity in experimental animals[16,17]. Details on TNF- inhibitory natural products have been reported earlier[7].

Cardiovascular natural products

A number of plants are reported to contain cardiac glycosides. Cardiac glycosides or cardenolides are steroidal in nature with an attached lactone group. They inhibit the membrane bound sodium-potassium ATPase pump resulting in depletion of intracellular potassium and an increase in serum potassium. This results in a decrease in the electrical conductivity through the heart tissue causing a decrease in the heart rate, and increasing cardiac output.

Yellow oleander plant (*Thevetia neriifolia*) is reported to contain thevitin A, B and peruvoside which are potent cardiac glycosides found in all parts of the plant and with high concentration in the fruits[18]. *Rauwolfia serpentina* was first tested in India for antihypertensive activity[19]. However, the active principle Reserpine was isolated and studied abroad[20,21]. It exhibits its action by inhibiting monoamine oxidase (MAO). *Terminalia arjuna* bark has been used for the treatment of symptoms similar to angina in the traditional Indian system of medicine. Arjunolic acid isolated from this plant has been shown to provide significant cardiac protection in isoproterenol induced myocardial necrosis in rats[22]. The *Coleus spp.* have been reported in the *Ayurvedic materia medica* for the treatment of heart diseases. Coleonol (or Forskolin as it is known now) isolated from this plant at CDRI, Lucknow[23], has been shown to possess hypotensive action and positive inotropic effect on the heart[24].

Anti-diabetic natural products

Diabetes is a widespread metabolic disease that affects around 41 million Indians and rightfully making it the 'Diabetic Capital of the World'. Several remedies are used since ages for the treatment of diabetes and similar disorders. The best example may be of Karela (*Momordica charantia*), which is widely used as a household remedy for the treatment of diabetes. Charantin, a steroidal saponin isolated from this plant is reported to have an insulin-like activity, responsible for its hypoglycemic effect. Besides, charantin stimulates the release of insulin and blocks glucose formation in the bloodstream, suggesting its beneficial effects in non-insulin-dependent diabetes[25].

Gymnema sylvestre (gurmar), is another plant that has been used traditionally for the treatment of diabetes. Gymnemic acid IV, obtained from leaves of *Gymnema sylvestre* has been reported to show strong hypoglycemic activity in animals models of diabetes comparable to glibenclamide[26]. Andrographolide, a diterpenoid lactone, isolated from *Andrographis paniculata* has been found to exhibit significant hypoglycemic activity[27].

Anti-obesity natural products

There has been a dramatic increase in prevalence of obesity with more than 1 billion adults overweight and at least 300 million of them clinically obese. The current clinical drugs for obesity are expensive and have several side effects associated with them. There are many remedies given in the Ayurveda and the *Shushruta Samhita* for the treatment of 'medroga' as it is referred to in these texts. Several natural products have also been studied for the anti-obesity action.

Tea polyphenolics like (-)-epigallocatechin 3,5-di-Ogallate (IC_{50}; 0.098 μ*M*), oolonghomobisflavan A (IC_{50}; 0.048 μ*M*), oolongtheanin 3'-O-gallate (IC_{50}; 0.068 μ*M*) and theaflavin 3,3'-O-gallate (IC_{50}; 0.092 μ*M*) show a potent pancreatic lipase inhibitory activity[28]. 3-Methyletherganglin and 5-hydroxy-7-(4'-hydroxy-3'-Methoxyphenyl)-1-phenyl-3-heptanone isolated from *Alpinia officinarum* have shown significant pancreatic lipase inhibitory activity *in vitro*. These compounds also showed a strong hypolipidemic effect in Triton WR-1339 induced hyperlipidemic mice[29,30]. Guggulipid, a fraction of *Commiphora mukul* resin has been developed at CDRI, Lucknow as a hyperlipidaemic agent[31,32]. Our previous reviews can be referred for further information on anti-obesity natural products[33,34].

Anti-malarial natural products

A number of medicinal plants have been used traditionally in the treatment of malaria. A variety of natural products have been isolated from these plants which have been reported for antimalarial activity. Several biflavonoids have been reported from *Selaginella bryopteris* which have been investigated for their anti-protozoal activity *in vitro* against K1 strain of *Plasmodium falciparum*. Out of these, bilobetin and heveaflavone showed maximum potency with an IC_{50} of 0.3 and 0.26 μ*M*, respectively[35]. Neem is widely used in the traditional Indian system of medicine for a variety of indications. Nimbolide has been identified as the active antimalarial principle of this plant (EC_{50}; 0.95 ng/ml, *P. falciparum* K1)[36]. Besides, gedunin (IC_{50} 720 ng/mL, *P. falciparum* D6) and its dihydro derivative have been found to be active (IC_{50}; 2630 ng/ml)[37]. Naphthylisoquinoline alkaloids isolated from leaves of *Ancistrocladus heyneanus*, particularly ancistrocladidine, ancistrotanzanine C and ancistroheynine B have been shown to exhibit significant anti-plasmodial activity with IC_{50} of 0.3, 0.1, and 0.5 μg/ml, respectively[38].

Anti-leishmanial natural products

Plant derived natural products have been used in traditional medicine as therapies for cutaneous leishmaniasis. A large number of molecules belonging to diverse classes of natural products have been isolated that have shown activity against either the promastigotes or amastigotes of *Leishmania* parasite. Diospyrin isolated from *Diospyros spp.* has been a very potent antileishmanial natural product with IC_{50} of 1μg/ml against *Leishmania donovani*[39], this compound was also found to inhibit the type I DNA topoisomerase of *L. donovani* parasite[40]. Plumbagin from *Plumbago spp*. is perhaps the most potent antileishmanial natural product with an IC_{50} of 0.42μg/ml against *L. donovani*[41]. Berberine from *Berberis aristata* also shows significant antileishmanial activity at IC_{50} of 10μg/ml against *Leishmania major*[42]. Piperine, which is found in many piper species, has been shown to be active against promastigotes of *L. donovani* with activity comparable to pentamidine[43]. Amarogentin, isolated from *Swertia chirata* has been found to inhibit *L. donovani* topoisomerase I[44].

Besides these compounds, Picroliv a standardized mixture of iridoid glycosides prepared from the root and rhizome extract of *Picrorrhiza kurroa* shows a significant antileishmanial activity and is used in combination therapy of *kala azar* with sodium stibogluconate. It is reported to enhance the efficacy of the antileishmanial drug and also to reduce its side effects[45]. Earlier publication on anti-leishmanial natural products can be referred for further information[46].

Anti-viral natural products

HIV is the leading cause of death in African continent and the disease is increasing at an alarming rate in India. Several natural products particularly alkaloids, phenolics and terpenes have shown a promising anti HIV activity. Theasinensin D, a phenolic compound found in tea (*Thea sinensis*) has

been shown to exhibit a good anti-HIV activity with IC_{50} of 8μg/ml[47]. The common phytosterols ursolic acid and oleanolic acid found in many plants has also been reported to show anti-HIV activity with an IC_{50} of 8μ*M* and 21.8μg/ml[48,49]. Gallic acid, chebulagic acid and other galloyl glucoses isolated from *Terminalia chebula* have been reported to show a promising HIV integrase inhibitory activity[50]. Termilignan, thannilignan, 7-hydroxy-3',4'-(Methy-lenedioxy)-flavone and anolignan B isolated from the fruit rinds of *Terminalia belerica* have been reported to possess demonstrable anti-HIV-1 acitivity[51]. For more detailed information on anti-HIV natural products a review published earlier on this subject can be consulted[52].

Anti-neoplastic natural products

A few of the Indian medicinal plants have also been studied for anticancer activity. Arnebin-I a napthoquinone found in *Arnebia nobilis* have been found to be active against Walker carcinoma in rats and P388 lymphoid leukaemia in mice models. A diterpenoid precalyone isolated from *Roylea calycina* has been reported to show activity against P388 lymphoid leukaemia[53]. The other compound studied for anticancer activity is Tagitinin F, a germacranolide isolated from *Tithonia tagitiflorahas* has been also found to be active against lymphocytic leukaemia[54]. Flavopiridol, a semi-synthetic flavonoid derived from rohitukine found in the plant *Dysoxylum binectariferum* is the first cyclin-dependent kinase (CDK) inhibitor to be tested in clinical trials[55,56]. Combretastatins found in species of *Combretaceae* family have reportedly been used in the treatment of cancer. Out of these Combretastatin A-4 has been found show a potent anti-angiogenetic action with a potent inhibition of tubulin polymerisation[57]. *Podophyllum emodii* has a long history of medicinal use in India, including the treatment of skin cancers and warts. Podophyllotoxin, a lignan isolated from this plant has been found to be responsible for the anticancer activity. A flavanol glycoside tephdidoside from *Tephrosia candida* has been found to be active against human epidermoid carcinoma of nasopharynx[58]. Echitamine chloride, an alkaloid from *Alstonia scholaris*, has been reported to show a dose-dependent regression of fibrosarcoma in rats. It has also been found to be active against P388 lymphocytic leukaemia in mice model[59]. Tylophorine an alkaloid isolated from *Tylophora indica*, has been reported to show antitumor activity in leukaemia model[60]. Parthenin, isolated from *Parthenium hysterophorus*, has been reported to show cytotoxic activity in human leucocyte chromosomes, erythrocytes of Swiss mice, and cultured bovine kidney cells[61,62].

Positive contributions from traditional medicines and a way forward

Besides the above mentioned applications of structurally defined natural products from Indian medicinal plants, they are also found useful in other diseases (Table 1). The '*kurchi*' plant (*Holarrhena antidysentrica)* has been used since ages for the treatment of dysentery. Conessine, a steroidal alkaloid, isolated from this plant is a well known example of anti-amoebic natural product. However, an important point to note is that the active principle, conessine, is itself toxic, but not the herb. The other example in this category is neoandrographolide from *Andrographis paniculata* which has been found to be active against bacillary dysentery and like kurchi is used as herbal medicinal formulation, but not its active constituent. *Adatoda vasica* is a well known anti-asthmatic, but vasicine the bioactive alkaloid from this plant still cannot fit the category of a drug. Brahmi (*Bacopa monnieri*) has been used since centuries as a memory enhancer. Baccosides isolated from these plants, however do not provide the similar results as the whole crude drug itself. Triphala has been used over centuries for cleansing of bowels and as a general well being tonic, however the individual constituents of the plants used in this formulation *i.e.* polyphenolics and tannins fail to exert the benefits that the whole formulation produces. The above mentioned but not exhaustive examples suggest that the traditional Ayurvedic plants have a tremendous potential clinically in their parent form and not as individual components. Hence, efforts towards better pharmaceutics should be directed to yield better formulations that can be helpful for a number of conditions. Apart from this, the standardization of the herbal medicinal products also needs improvement and more stringent control as for the allopathic medicinal system.

Other important applications of Indian natural products

Natural products, besides being source of leads for a number of drugs also play an important role in the industrial drug synthesis. This is because of the presence of a wide chemical diversity in natural

Table 1—Natural products from Indian medicinal plants and their biological activity

Plant/Herbal formulation	Chemical constituents	Biological activity/Indication	Marketed/Traditional formulation
Adhatoda vasica	Vasicine, vasicinone	Bronchodilator	Diakof®, Koflet®
Euphorbia prostrata	Flavonoids	Piles	Thank God®
Cassia spp.	Sennosides	Constipation	Kayamchurna®
Bacopa monnieri	Baccosides	Memory enhancer	Mentat®, Himalaya Brahmi®
Tylophora indica	Tylophorine	Bronchodilator	Fizzle®, Vasa forte®
Triphala	Polyphenolics, Tannins	Bowel cleanser, general tonic	Triphala
Holarrhena antidysentrica	Conessine	Antiamoebic	Kutajarista
Asparagus adscendens	Asparanin A, Asparanin B, Sarasapogenin	Fertility enhancer	Spermon®
Asparagus racemosus	Shatavarin	Galactogogue, tonic	Geriforte®
Ocimum sanctum	Monoterpenes, sesquiterpenes	Respiratory diseases, immunomodulatory	Kofostal® syrup, Curill® capsules
Glycyrrhiza glabra	Glycrrhizin	Antiulcer, anti-tussive	Kofex®
Aloe vera	Aloin	Demulcent, skin diseases	Clarina®
Tribulus terrestris	Protodioscin	Diuretic, anabolic, aphrodisiac	Gokshura
Trigonella foenum-graecum	Trigonellin	Anti-diabetic, lipid lowering	Ayuslim®
Withania somnifera	Withanolides	Immunomodulatory	Ashwagandharista
Embelia ribes	Embelia	Anti-fertility	Pipalayadi yoga
Pterocarpus marsupium	Liquiritigenin, isoliquiritigenin	Anti-diabetic	Diabecon®
Tinospora cordifolia	Tinosporic acid, Cordifolioside	Immunomodulatory	Himalaya Guduchi®
Aegle marmelos	Aegelin, Marmelosin	Bowel diseases	Diarex®
Phyllanthus emblica	Polyphenolics, Tannins	Antioxidant	Chyavanprasha
Centella asiatica	Asiaticoside	Memory enhancer	Mentat®
Garcinia cambogia	Hydroxycitric acid	Antiobesity	Bioslim®, Ayuslim®
Psoralea corylifolia	Psoralen	Vitiligo	Pigmento®
Areca catechu	Tannins	Antiobesity, anti-tussive	Koflet®, Bioslim®
Gmelina arborea	Arboreol	Tonic, stomachic	Chyavanprasha
Achyranthes aspera	Achyranthine	Diuretic	Cystone®
Antethum graveolens	Anethole	Digestive, carminative	Bonnisan®
Argyreia nervosa	Alkaloids	Aphrodisiac, fertility enhancer	Confido®
Vitex negundo	Flavonoids	Antiinflammatory	Himcolin®
Bahuhinia variegata	Flavonoids	Diarrohoea, piles	Pilex®
Boerrhavia diffusa	Boeravinones	Hepatoprotective	Liv 52®
Cyperus rotundus	Monoterpenes, Sesquiterpenes	Antibacterial, antipyretic	Himpyrin®
Evolvulus alsinoides	Flavonoids	Bitter, tonic	Anxocare®
Symplocos racemosa	Alkaloids	Gynaecological disorders	Evecare®
Eugenia jambolena	Anthocyanins	Anti-diabetic	Diabecon®

products, which enables them to be starting materials for several stereospecific reactions. The latest example of this case would be of oseltamivir (Tamiflu) which is the only cure available for treatment of Swine flu caused by H1N1 virus. For the synthesis of this drug, shikimic acid is used as a starting material which is obtained from Chinese star anise. A recent study reveals that this compound is present in high yields in Indian plants such as *Calophyllum apetalum* (4.10% shikimic acid by dry weight) and *Araucaria excelsa* (5.02% shikimic acid by dry weight), which can be used as an alternative source of shikimic acid[63]. Natural products also act as bioavailability enhancers in many cases by inhibiting the drug metabolizing enzymes. Piperine, an alkaloid found in various *Piper spp.* has been found to enhance the bioavailability of a number of drugs[64]. Stevioside found in *Stevia rebaudiana* is a glycoside that is 300 times sweeter than sucrose and hence finds an important application as a sweetening agent[65].

Conclusion

Indian medicinal plants have contributed a great deal to the academic curiosity as it is apparent from the number of publications, but could not provide breakthrough molecules such as paclitaxel and

artemisinin for drug discovery. The credits for the leads like reserpine and forskolin earlier obtained from the plants of traditional Indian system of medicine had been taken by the western pharmaceutical companies. Still indigenous systems of medicines have a great scope for the discovery of leads for several disease classes by the virtue of the chemical and biological diversity. The potential of finding novel bioactive compounds that act synergistically with less active molecules is much higher from traditional medicines. These chemicals can unlock new chemistry and biology to discover new drugs.

It may be mentioned that hundreds of plant metabolites are reported to have *in vitro* anti-viral and anti-cancer activity, but the specific activities of the pure compounds is usually 2-3 orders of magnitude below the required therapeutic levels. Thereby, the daily dose requirements become very high to ensure adequate plasma levels, doses of which range from 40-60g per day of crude extracts or constituent(s), which is virtually impossible and in many cases toxic. The problem is compounded further by solubility and other ADME problems. The best example is curcumin which has been studied extensively for wound healing, anti-microbial, anti-fungal, anti-HIV, anti-cancer and lipid lowering activities at cellular and molecular levels, but could not be incorporated in the physician's arsenal. Therefore, the development of traditional medicines has to be done by keeping in view the targeted therapeutic area. The best suited areas for traditional medicines can be metabolic and some inflammatory diseases, whereas the search for NCEs for cancer, viral including HIV, etc can be done from Indian medicinal plants.

There is also a need to develop and screen a large number of pure compound and plant extract libraries to make the most out of what is available. Besides this approach, semi-synthetic modifications can also be attempted for the existing hits to get better lead compounds from the natural products. These approaches can surely be a driving force for the drug discovery from Indian medicinal plants and lead to fruitful results for mankind.

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