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Perspective paper

Trends in ethnopharmacology

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Abstract

The use of plants, plant extracts or plant-derived pure chemicals to treat disease is a therapeutic modality, which has stood the test of time. Indeed today many pharmacological classes of drugs include a natural product prototype. Aspirin, atropine, ephedrine, digoxin, morphine, quinine, reserpine and tubocurarine are a few examples of drugs, which were originally discovered through the study of traditional cures and folk knowledge of indigenous people. There is a revival of interest in herbal products (botanicals) at a global level and the conventional medicine is now beginning to accept the use of botanicals once they are scientifically validated. *Ispaghula*, *Garlic*, *Ginseng*, *Ginger*, *Ginkgo*, *St. John's Wort*, and *Saw palmetto* are a few examples of botanicals which are gaining popularity amongst modern physicians and this trend is likely to continue partly due to high cost involved in the development of patentable chemical drugs. There is growing evidence to show that medicinal plants contain synergistic and/or side-effects neutralizing combinations. Ethnopharmacology has already played important role in the development of conventional medicine and is likely to play more significant role in the years to come. A team work amongst ethnobotanists, ethnopharmacologists, physicians and phytochemists is essential for the fruitful outcome on medicinal plants research. While the ethnopharmacologists have a greater role to play in the rationalization of combination of activities, the phytochemist's role will slightly shift towards standardization of botanicals.

Keywords: Medicinal plants; Ethnopharmacology; Synergistic and side-effects neutralizing combinations

1. Historical aspects

According to the world health organization (WHO), about three-quarters of the world population relies upon traditional remedies (mainly herbs) for the health care of its people. In fact, herbs/plants are the oldest friends of mankind. They not only provided food and shelter but also served the humanity to cure different ailments. The herbal medicine also sometime called as, traditional or natural medicine existed in one way or another in different cultures/civilizations, such as Egyptians, Western, Chinese, Kampo (Japan) and Greco-Arab or Unani/Tibb (south Asia).

Historians from all around the world have produced evidence to show that apparently all primitive peoples used herbs-often in a sophisticated way. Quinine from Cinchona bark was used to treat the symptoms of malaria long before the disease was identified and the raw ingredients of a common or garden aspirin tablet have been a popular painkiller for far longer than we have had access to tablet-making machinery.

By the middle of the nineteenth century at least 80% of all medicines were derived from herbs. Then came the revolution inspired by the development of the pharmaceutical industry and synthetic drugs dominated, though herbal medicine has never been out of scene. Even today if you walk into any pharmacy in the West, you will find at least 25% plant-derived drugs. Indeed today many pharmacological classes of drugs include a natural product prototype (Gilani et al., 1992). Aspirin, atropine, artimesinin, colchicine, digoxin, ephedrine, morphine, physostigmine, pilocarpine, quinine, quinidine, reserpine, taxol, tubocurarine, vincristine, and vinblastine are a few examples of what medicinal plants have

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given us in the past. Most of these plant-derived drugs were originally discovered through the study of traditional cures and folk knowledge of indigenous people and some of these could not be substituted despite the enormous advancement in synthetic chemistry.

Morphine isolated from the opium poppy (*Papaver somniferum)* is one of the early molecules entered into conventional medicine and is the humanity's finest painkiller. Only the cancer patients suffering from terminal pain can appreciate the value of morphine, which remains drug of choice today despite its abuse potential. Indeed, the isolation of morphine from crude opium by Serturner in 1806 stimulated so much wide-spread research on the vegetable drugs that Megendie was able to publish a medical formulary in 1821, which contained only pure chemical agents, hence laid the foundation for the use of pure chemicals as the alternative to the botanicals.

One of the important areas in which compounds from plant sources have contributed successfully is cardiovascular research (Gilani, 1998). Digitalis and the cardiac glycoside derived from the foxglove (*Digitalis purpurea*) are perhaps the classic example. They represent a widely used group of clinically effective compounds which produce positive inotropic effect on the failing heart as well as having value in the treatment of atrial fibrillation. As a group they are unrivalled to date by any synthetic or semi-synthetic substitutes even though they are among the most toxic group of clinically useful drugs and have unique mode of action with selective cardiotonic activity, without accompanying tachycardia (Rietbrock and Woodcock, 1985).

A second discovery of cardiovascular activity in natural products led to the isolation of reserpine over five decades ago. Reserpine, obtained from the roots of the Indian plant *Rauwolfia serpentine*, was brought to the attention of the modern Western world in 1949 by Vakil who described its use in hypertension; in rapid succession between 1952 and 1958, reserpine was isolated from *Rauwolfia*, its structure determined and its total synthesis achieved (Dohadwalla, 1985). The indiscriminate use of reserpine as an antihypertensive agent and tranquilizer led to reports of depression and Parkinsonism effects. These findings stimulated further investigation and evidence was found that reserpine depleted not only brain serotonin but also nor-epinephrine and dopamine (Curzon, 1990). This was a major stimulus for continued research on transmitter amine defects in depression and Parkinson's disease. This in part laid the foundation for the development of many of the modern psychoactive drugs and stimulated a significant interaction between researchers and drug industry.

As the adverse effects of reserpine continued to be revealed through clinical research, interest in the product gradually diminished, particularly when safer antihypertensive drugs were made available, though reserpine is still used in clinical medicine, particularly in low-income population. In deed, there is a revival of interest in its use based on some recent clinical trials, which showed that lower doses of reserpine (0.05–0.1 mg) combined with low doses of thiazide diuretic and hydralazine provides highly effective blood pressure lowering regimen along with renal protective effect; relatively free from conventional side-effects and is perhaps the most cost-effective antihypertensive treatment available today (Pavan et al., 2003; Milne and Pinkney-Atkinson, 2004).

This development of reserpine clearly illustrates the fundamental scientific principle that drugs, in addition to being therapeutic agent, become tools for further understanding of disease and hence design of new drugs. Other compounds, which are considered invaluable pharmacological "tools" for evaluating the mode of action of other drugs or investigation of basic physiological function, include muscarine and nicotine (pioneer selective agonists for muscarinic and nicotinic receptors respectively), cocaine (catecholamine uptake inhibitor) yohimbine (selective α_2 blocker) and himbacine, a prototype of cardio-selective antimuscarinic agents (Gilani, 1998).

Aspirin, an acetyl salt of salicylic acid (an active principle from Willow bark) is considered one of the most effective analgesic, antipyretic and anti-inflammatory agents commonly used in modern medicine. With the passage of time multiple therapeutic uses of aspirin have been emerged, with most prevalent use as the antiplatelet/anticoagulant observed at the low dose to prevent further problems in patients who have already suffered from one heart attack (Saeed et al., 2002).

The major antithrombotic drugs used today all derived from veterinary practice in Canada in the 1920s when cattle were noticed to be developing stomach haemorrhage from eating mouldy hay containing sweet clover (*Melilotus officinalis*). Freshly-cut hay contains sweet smelling coumarins, many of which act as anticoagulants. Dicoumarol was the major drug synthesized as a result of these observations. It was first marketed by Abbot and Lilly in 1942. Warfarin (from *Melilotus officinalis*) has been known to most people since the 1940s as a rat poison that acts through its anticoagulant action. The unsuccessful suicide attempt by a US Army recruit showed it to be a less toxic anticoagulant than the dicoumarol and therefore for human use (Minter, 2001). Warfarin so named from the Wiscounsin Alumni Research Foundation who received the royalty from the drug sales is the world's most successful anticoagulant drug, used in cardiology, stroke, and in general post-operative recovery when a patient is at risk from clotting during bed rest.

2. Revival of interest in phytomedicine

Despite the increasing interest of public in phytomedicine, very few drugs from higher plants have attained any prominence in conventional medical practice in the last couple of decades. The most notable example is Taxol, a diterpenoid originally obtained from the bark of the Pacific yew tree (*Taxux brevifolia* Nutt.*)*. However, even this effective

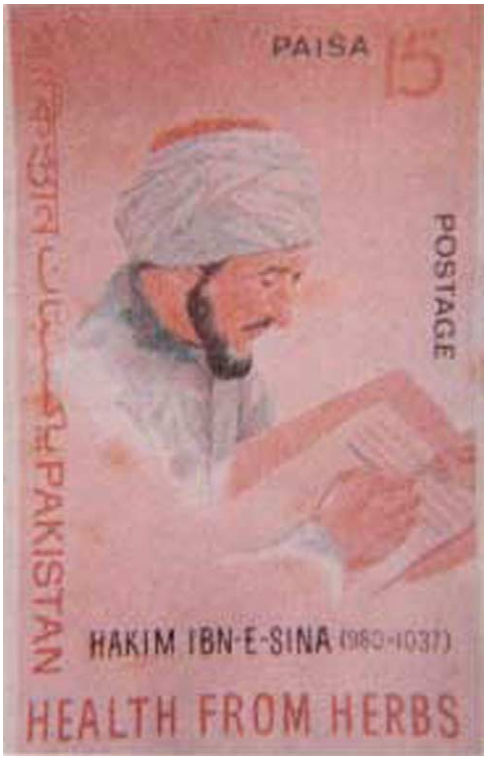
anticancer agent is now produced by semi-synthesis from a precursor occurring in the needles of the common yew (*Taxux baccata* L.), a rapidly renewable source (Rao et al., 1995). Instead, major progress in the last decade has been in the field of phytomedicine, also referred to as botanicals or herbal medicine. In Germany and many European countries, these products are classified as drugs; in USA they are sold as dietary supplements.

There is a clear evidence of revival of interest in phytomedicine at a global level, the revival which has been so dramatic that sales of herbal products in the world worth staggering over 100 billions dollars a year. East is already well known for its adherence to herbal medicine and China and India are two leading countries in this regard. Even in the western world, popularity of the phytomedicine is increasing at a rapid pace. Germany is the leading country in Europe followed by France in the use of botanicals. Around 80% of German physicians prescribe herbs and St. John's Wort is a commonly prescribed in mild to moderate depression. Similarly, *Ginkgo* is a hot selling botanical in Europe. The cost of about 40% of the herbal remedies prescribed by German physicians is covered by the health-care system (Harrison, 1998). In USA a large Center of Complimentary and Alternate Medicine has been established recently at the NIH, with heavy funding (Jones, 1998) and more recently, NIH has been engaged in sponsoring studies on large clinical trials on botanicals such as, *St. John's Wort* and *Ginkgo*.

The conventional medicine is now beginning to accept the use of botanicals once they are scientifically validated. *Ispaghula*, *Garlic*, *Ginseng*, *Ginger*, *Gingko*, *St. John's Wort* and *Saw palmetto* are a few examples of botanicals which are gaining popularity amongst modern physicians. Similarly, studies on medicinal plants particularly on the biological aspects and the impact factor of the journals publishing such research are growing with rapid pace. One can imagine the popularity of herbal medicine in the west from the fact that an American Journal of Chinese Medicine exists in the literature. There is an increasing trend in the north America and Europe to incorporate the complementary and alternative medicine, particularly the herbs as an essential component in the medical curriculum (Wetzel et al., 2003).

In line with the revival of interest in the old remedies, there is also greater recognition of the scholarly work of the physicians of olden days. British Pharmacology Society (BPS) recently decided to publish regularly in its Bulletin the postage stamps that portray the images of famous physicians of the past. Interestingly, the old famous stamp on herbal medicine issued by the Pakistan Post with an image of Ibn Sina (981–1037 C.E.), known as, Avicena in the west, occupied first place in this series (BPS Bulletin Spring issue 2001, www.bps.ac.uk). Ibn Sina authored one of the most famous books, al-Qanun fi al-Tibb, known as "Canon" in the west, which is considered an immense encyclopedia of medicine and remained supreme for over six centuries because of its systematic approach, formal perfection and intrinsic value. He laid the foundation of the Greco-Arab system of herbal medicine (Unani Tibb), based on the philosophy of individualized treatment considering the genetic variations amongst the individuals, similar to the concept of Pharmacogenetics in conventional medicine.

The concept of side-effects and the individualized treatment is perhaps more effectively elaborated in the traditional medicine (Unani Tibb), where even herbal products, like ispaghula (which is considered probably the safest by the modern physicians) is not necessarily free from side-effects, rather known to rarely cause numbness and impotence (unless combined with honey) if used regularly by the older people in the cold weather. The old concept that it is not the "safe medicine", rather the "safe physician" or the "safe use" that matters in therapeutics, is getting strength. It should be born in mind that botanicals (mixtures of multiple chemicals) are more likely to cause individual variation in actual clinical situation than the pure compounds derived from plants. It is not surprising that the herbal remedies have been classified according to the four main temperaments (mizaj) of the individuals particularly in the Unani Tibb and such aspects may be considered when planning clinical trials on herbal products.



It is well known fact that the plants grown in different climatic conditions may contain different chemical composition of active principles; hence it is not surprising that the folkloric use of a plant can vary in different geographical origins. For example, *Caesalpinia bonduc* has been used in Africa as a uterine stimulant, and this effect was shown to be mediated through cholinergic effect (Datte et al., 1998), where as in south Asia this plant is used as an antispasmodic

and antidiarrhoeals, and here it was observed that the plant contains predominantly antispasmodic constituent(s) mediated through calcium channel blockade in addition to a minor cholinergic component (Jabeen, 2001). Thus, the ethnobotanical use of the plants in relation to their origin may be important when developing botanicals for the healthcare purpose and also warrants standardization.

In addition to the exclusive use of medicinal plants in treating disease, unique herbo-mineral preparations, locally known as "Kushta(s)" have also been used in the traditional medicine system of Indo-Pak subcontinent (Unani Tibb and Ayurveda). These preparations have long been used and claimed to be the most potent and effective dosage forms. However, there are only few scientific studies carried out on these products because of several reasons mainly being the lack of communication amongst traditional healers, physicians and scientists. We have tried to fill this gap by translating the old concepts in modern understanding providing possible explanation and hypothesis (Aziz et al., 2002) and it is hoped that these important group of traditional remedies will attract further attention of the scientific community in the years to come.

3. Synergistic and/or side-effects nullifying combinations in plants

The presence of synergistic and/or side-effects neutralizing combinations in medicinal plants is an old concept put forth by the Hippocrates and strengthened by Ibn Sina and others; however, this concept remained dormant and lacks sufficient scientific evidence mainly due to scarcity of ethnopharmacologists with wider background. Our group is actively involved on a wide range of biological assays with closely observing the significance of such combinations of activities in plants. Interestingly, we found some interesting combinations and observed that acetylcholine (Ach) and calcium channel blockers (CCB)-like activities are abundantly present in plants and usually co-exist in most of the plants studied (Ghayur et al., 2005; Gilani et al., 2000a, 2005, 2005a, 2005e). While CCBs are well known for their therapeutic use in the cardiovascular disorders, with potential in a wide range of diseases, including asthma and cough, premature labor, diarrhea and abdominal spasms, gastric ulcers, and neurological disorders, such as migraine, epilepsy, depression, mood disorders and Alzheimer's' disease, etc., however, acetylcholine-like drugs have limited use in modern therapeutics despite the fact, Ach is one of the most important neurotransmitters in our body without which life is almost impossible. This is mainly because of brief and wide spread actions of Ach in the whole body leading to multiple side-effects, as opposed to the localized effect when released physiologically.

Selective action of a drug on the particular organ system is important for the safe therapeutic use, which is usually achieved in modern therapeutics through discovering drugs selectively stimulating (agonist) or blocking (antagonist) the specific receptors. Based on our pioneer work on the subtypes of muscarinic receptors, we were successful in reporting plant-derived drug himabicine, as a prototype of a cardioselective antimuscarinic drugs (Gilani and Cobbin, 1986) and latter another such plant-derived drug, ebeinone (Atta-ur-Rahman et al., 1994; Gilani et al., 1997), however, there is scarcity of selective agonists for Ach receptors; hence a limited role of cholinergic drugs in therapeutics.

An alternate approach to achieve cholinergic effect is through inhibition of an endogenous enzyme (ACE), responsible for the breakdown of endogenous Ach, thus making availability of enhanced level of Ach at the desired site, as is the case for the use of ACE inhibitors in myasthenia gravis, senile dementia and Alzheimer's disease (AD). We have some success in reporting the presence of ACE inhibitory substances in medicinal plants (Atta-ur-Rahman and Choudhary, 2001; Khalid et al., 2004; Gilani et al., 2004, 2005b) and thus provided scientific explanation for some of the traditional uses of the respective medicinal plants. Recently it was reported that calcium antagonists are also useful in AD and we provided the first evidence for the presence of additional activity (ACE inhibitory) in a well known calcium antagonist, verapamil (Gilani et al., 2005b) thus making it a very good candidate for its use in AD. Interestingly, the presence of a unique combination of activities (ACE inhibitory and calcium antagonist) was found in *Sarcococca saligna* with active chemicals identified (Khalid et al., 2004; Gilani et al., 2005b). Similarly, juliflorine from *Prosopis juliflora* and Withanolides from *Withania somnifera* were found to possess this unique combination of activities (Choudhary et al., 2005, 2005a). These studies points towards the therapeutic potential of such plants, or their active chemicals (with dual action) in AD.

Chronic constipation is a gut disorder, for which even modern medicine relies upon herbal products. Psyllium husk (ispaghula) is a unique product in two ways: (1) it is equally acceptable in traditional and modern medicine as the first line treatment for such disorders and (2) it is considered equally effective in the traditional medicine for its use in constipation and diarrhoea, two opposite disease states of the gut. The general perception is that its laxative effect is achieved mainly through its fiber contents, which may be true but what it makes more effective than other fiber containing remedies is not clear. We provided the first evidence that it also contains chemical(s) with gut stimulatory effect mediated partly through cholinergic activation (Gilani et al., 1998a), which is likely to supplement the laxative effect that makes it treatment of choice in chronic constipation. Interestingly, it also contains gut inhibitory constituent(s), which not only is/are likely to offset the side-effects associated with cholinergic components but also provides scientific explanation for the traditional use of ispaghula in diarrhoea (Gilani et al., 1998b). We recently reported that in addition to gut stimulatory and inhibitory constituents likely to be responsible for its usefulness in constipation and diarrhea respectively,

it also contains antiamoebic constituent explaining its traditional use in amoebic dysentery (Zaman et al., 2002), thus making this a unique product with combination of multiple activities. This study is in progress to identify the nature of chemicals responsible for different activities in this unique product.

While Ach plays important physiological role in maintaining the peristaltic movements of the gut for the normal bowel habits, no such drugs is used in therapeutics for laxative therapy because a slightly higher dose leads to abdominal cramps along with other side-effects due to its non-selective action. Hence the presence of a unique combination of gut stimulatory and inhibitory constituents in ispaghul and in a few other plants, such as *Prunus persica* (Gilani et al., 2000a,b), *Piper betle* (Gilani et al., 2000a,b), *Fumaria indica* (Gilani et al., 2005), *Hibiscus rosasinensis* (Gilani et al., 2005a) and ginger (Ghayur and Gilani, 2005) depicts interesting story. Interestingly, the stimulatory effect was more evident in constipated gut (stretched ileum in these experiments) and the inhibitory constituents become more active in the hyperactive gut, like spontaneously contracting rabbit jejunum preparation. In addition, the presence of latter inhibitory effect seen at a relatively high dose, does not allow the stimulatory effect to go beyond certain limit, above which the cholinergic activity is likely to produce abdominal cramps, a usual characteristic of laxative therapy with chemical drugs.

Interestingly, medicinal plants such as, *Sesamum indicum*, *Lavandula stoechas*, ginger and *Carum copticum* which have been used traditionally for lowering of blood pressure (BP) were found to mediate this effect through a combination of CCB and Ach-like activities (Gilani, 2001; Ghayur et al., 2005; Gilani et al., 2005c). Calcium channel blockers and cholinergic drugs are known to mediate similar effect (both are inhibitory) in the cardiovascular system, while with opposing effect (Ach excitatory and CCBs inhibitory) in most of the other systems, such as respiratory, gastrointestinal and renal etc. This combination of activities may provide lead to design experiments for testing clinical usefulness of some of the existing drugs in these categories.

Turmeric (rhizome of *Curcuma longa*) has been traditionally used as antispasmodic and bronchodilator in addition to other multiple uses. In an attempt to provide scientific basis for such use we demonstrated that turmeric elicits these activities through CCB (Gilani et al., 2005d) and phosphodiesterase (PDE) inhibitory activity (unpublished data). However, when tested for its blood pressure lowering effect in rats under anesthesia, it was found devoid of any clear effect with indication for the presence of both hyper and hypotensive components. In isolated tissue experiments on vascular preparations, it was confirmed that it contains two components with opposing activities (vasodilator and vasoconstrictor) thus explaining the lack of traditional use in hypertension despite the presence of calcium channel blockers. When curcumin the main active compound of turmeric was tested, it showed exclusive CCB activity in different gut, tracheal and cardiovascular preparations with no vasoconstrictor component seen indicating that curcumin, is not necessarily a true representative of turmeric in all respects and that the folkloric use of botanicals for healthcare is based on meaningful explanation.

St. John's Wort (*Hypericum perforatum)* is a popular botanical used for mild to moderate depression and its antidepressant actions are believed to be mediated through multiple modes, such as inhibition of monoamine oxidase, catechol-o-methyltransferase and dopamine-β-hydroxylase (Thiede and Walper, 1994; Kleber et al., 1999; Ron et al., 2000), by blocking synaptic reuptake of 5-HT, noradrenaline, dopamine, GABA and L-glutamate (Muller, 2003), inhibiting nitric oxide synthase (Luo et al., 2004) and through calcium channel and PDE blockade (Gilani et al., 2005e) and it is possible that the botanicals acting through multiple sites of action require less dose for the net effect; hence with less side-effects. We recently studied John's Wort to explain its folkloric use as antispasmodic and bronchodilator, and it was observed that these smooth muscle relaxant effects are mediated through a combination of CCB and PDE inhibitory-like constituents (Gilani et al., 2005e), which are known to exert opposing effects in the heart. In addition, it also contains two components with opposing activities (vasodilator and vasoconstrictor) with no significant net effect on the blood pressure, similar to what we observed in turmeric (Gilani et al., 2005d), thus explaining the lack of its traditional use in hypertension despite the presence of calcium channel blockers.

All these examples indicate that the plants in their crude form show interesting combination of activities and there is a huge potential of medicinal plants not only as a source of new drugs but also their use in the form of botanicals both in developing countries and the industrialized world. Ethnopharmacology has already played important role in the development of conventional medicine and is likely to play more significant role in the years to come. It would not be surprising to see that the use of botanicals will be gradually accepted in the main stream of conventional medicine particularly if some mechanism of royalty comes into practice. A team work amongst ethnobotanists, ethnopharmacologists, physicians and phytochemists is essential for the fruitful outcome on medicinal plants research. The ethnopharmacologists will play more effective role in studying the rationale for the presence of different combinations of activities in individual medicinal plants as well as in the compound formulations, while phytochemist's role will slightly shift towards the standardization of botanicals.

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