Folk medicine meets metabolomics and public health

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A recent issue of *Current Science*[1] reported the emergence of a new discipline, i.e. metabolomics. Humans have been using aspirin, quinine and other secondary metabolites as plant extracts for a long time now. However, it was only in the last century that we started identifying, isolating and, later, synthesizing the active compounds that have therapeutic value.

The discovery of penicillin, a secondary metabolite from a fungus, brought about a revolution in health care. Though a quick succession of discoveries led to a wide variety of other antibiotics and chemical modifications of these antibiotics produced an even wider range, the emergence of resistant strains of bacteria has started to threaten world health-care systems. It is in this context that we explore recent Indian advances in metabolomics that shed light on folk and traditional medicines.

Take the example of the peepal tree. The bark and leaves of *Ficus religiosa*, or the Bodhi tree, are recognized for their antibacterial, antifungal, antiviral, antiulcer and antidiabetic properties. They are extensively used in ethnic medicine to treat sexually transmitted infections such as gonorrhoea, genital ulcers and skin diseases. However, an empirical study to test the antiviral activity on *Herpes simplex* was lacking.

Recently, scientists from the Birla Institute of Technology, Ranchi and the University of Torino, Italy, together explored the utility of a traditional Ayurvedic medicine in treating the herpes simplex infection[2].

The research team used the bark extracts in water and chloroform. They screened the extracts to identify the essential bioactive metabolites. Virucidal assays were conducted with the extracts to assess their possible virus-inactivating property.

The scientists found that the bark extract in chloroform was effective in inhibiting the early steps of the replicative cycle. They also confirmed the inhibition of attachment and entry of virus with viral yield reduction assays. However, this extract did not inactivate extracellular virus particles.

The water bark extract, on the other hand, was found to directly inactivate the infectivity of HSV-2 virus particles.

These results help us understand the mode of antiviral action of peepal bark extracts. *F. religiosa* offers therapeutic benefits to cure *H. simplex* infections. However, further studies are required to assess its effectiveness in clinical settings.

HSV-2 is a sexually transmitted disease. The global prevalence of HSV-2 infections in the 15–49 age group is estimated to be 11.3% (ref. 3). The infection is mostly asymptomatic and occasionally causes genital ulcers and sores. Though there are antiviral drugs that target the viral DNA, there is no permanent cure. The infection persists lifelong. Thus new antiviral sources are sorely needed.

Peepal is only one example from which such antivirals may be derived. There are many more plants in traditional medicine which need investigation.

Plants are not the only potential sources for medicines of the future. Several novel bioactive compounds have been discovered from actinomycetes. Recently, researchers from the SRM University, Chennai and the Sri Muthukumaran Research Institute, Kattankulathur, have identified bioactive secondary metabolites produced by microbes from the discarded solid waste of tanneries[4].

The rumen of herbivores has an bacterium, *Paracoccus pantotrophus*. The bacteria produce a wide range of secondary metabolites: antibiotics, antitumour agents, immunosuppressants, herbicides, pesticides, anti-parasitic agents and enzymes. Yet, the antibacterial activities of crude bioactive compounds against multidrug-resistant organisms are not known, and the pharmacological and toxicological effects on humans and animals have not yet been studied.

The researchers performed rapid hydrolysis of animal fleshing. They characterized the chemical composition of the crude extract of the bioactive compound from rumen bacteria, *P. pantotrophus* FMR19 in hexane fraction using gas chromatography–mass spectrometry analysis. The major components found in the extract include long-chain fractions of hexane, fatty alcohols, fatty acid, methyl ester and aromatic hydrocarbons. Among these, scientists identified eight major compounds that had antioxidant, cytotoxic and antimicrobial properties.

The hexane fraction showed inhibition against clinical pathogens such as *Salmonella* sp. and *Proteus* sp. They were found to be effective on multidrug-resistant pathogens such as metallo-beta-lactamase, pandrug-resistant bacterial strains and Methicillin-resistant *Staphylococcus aureus*. In fact, the hexane fractions were more active against multidrug-resistant organisms than against other clinical pathogens.

Tanneries are a cheap and easily accessible source for the production of an appreciable level of bioactive compounds. Therefore, the raw material for the production of future antibacterials is assured.

The dietary reluctance to animal fleshing can be overcome by industrial production of *P. pantotrophus*. However, the translation of these results to the pharmaceutical industry would involve extensive clinical trials.

The case of *P. pantotrophus* is not isolated. Animals have natural immunity to many pathogens. Leveraging on this knowledge, we could identify more such non-toxic antibacterials and antifungals from animal sources to counter the challenge of infectious pathogens.

It is not only in plants, animals and microorganisms that we should seek new therapeutics. A large number of traditional foods and beverages also contain metabolomics secrets that need unlocking. Take, for instance, the case of kombucha. It is an oriental beverage prepared by fermenting sugared black tea using a symbiotic culture of acetic acid bacteria and yeast. This ‘combo-chai’ is claimed to have various positive effects on bioregulatory functions. The polyphenolic compounds and flavonoids in green or black tea are known for their potent antimicrobial and antioxidative properties. However, screening of the effective and active constituents in kombucha has not been done.

A team of researchers from Jadavpur University, the National Institute for Cholera and Enteric Diseases and the Bose Institute, Kolkata, tested the

antibacterial activity of kombucha after different durations of fermentation[5]. They determined the minimal concentration for the inhibition of bacterial growth by measuring the diameter of the inhibition zone in the culture medium.

They found that kombucha fermented for 14 days showed maximum bacteriostatic and bactericidal activities. Using HPLC, they identified catechin and isorhamnetin as the major antibacterial polyphenolic compounds in kombucha. Though catechin is present in tea, isorhamnetin is only formed due to the fermentation process.

Kombucha is an effective and cheap source of polyphenols, which can be easily prepared at home. However, here too, further rigorous clinical evaluation is essential in order to promote it as a bactericidal for enteric infections. In the meantime, we may use it as a neutraceutical at home.

The cases of peepal, animal rumen and kombucha are examples of the kind of transformations that are taking place in the area of translational research. Given the tools – gas chromatography–mass spectrometry, HPLC – and the recent improvements in databases of chemicals, it has become easier than ever before to deal with the chemical complexities of traditional medicine. The time is now ripe for a concerted effort to identify the active components of folk and traditional medicine. This needs to be undertaken as a collaborative effort similar to the Human Genome Project.

For example, Patil *et al.*[6] observed the presence of *Vorticella* spp., a genus of ciliated protozoa, in water collected in their neighbourhood in Maharashtra. They explored the possibility of *Vorticella* spp. as a prospective mosquito biocontrol agent.

They collected 1st, 2nd, 3rd and 4th instar larvae of *Aedes aegypti* and *Anopheles stephensi* from nearby marshy places and stagnant ponds, and studied the effects of *Vorticella* spp. on larval development.

The team found that the 1st and 2nd larval instars of both *An. stephensi* and *Ae. aegypti* did not show signs of infection by *Vorticella* spp. The 3rd instars of *An. stephensi* showed more *Vorticella* infection than those of *Ae. aegypti*. However, 4th larval instars of both mosquitoes were heavily infected with *Vorticella*. The infection caused sluggish movements of larvae and eventually death. *Vorticella* spp. was responsible for more than 90% reduction in adult emergence for both *An. stephensi* and *Ae. aegypti*. The study provides insights into the larvicidal action of the surface parasite *Vorticella* on the different larval stages of *An. stephensi* and *Ae. aegypti*.

Mosquitoes are vectors of many human diseases, transmitting malaria, lymphatic filariasis, encephalitis and arboviruses such as dengue and zika. Vector control is still the main form of prevention for these diseases. Chemical methods of controlling the vector population have led to environmental problems. Biological control agents are thus becoming an important tool in mosquito control. They are eco-friendly as well as highly effective. Also, It will not take too much effort to find the most effective *Vorticella* species for this purpose.

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