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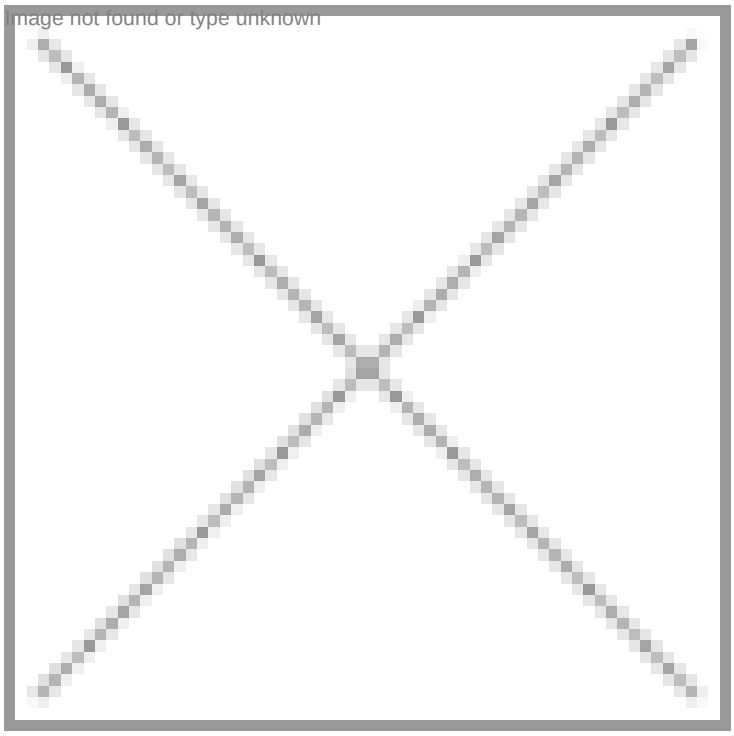

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Scientists from the National Institute of Oceanography, Goa in collaboration with researchers at the National Centre for Cell Science, Pune, and International Centre for Generic Engineering and Biotechnology, have isolated two anti-malarial molecules from mussels and these molecules may be used in conjunction with conventional drugs.

Pre-clinical toxicity study of the molecules have shown absolutely no side effect. Clinical trials will begin in two months.

The Council of Scientific and Industrial Research (CSIR) has been assigned a US patent for the discovery of two promising compounds NIO-1 and NIO-2 from mussels for the treatment of malaria. This discovery has been made by Dr Anil Chatterji, scientist, National Institute of Oceanography (NIO), Goa-a CSIR institute, along with researchers from the National Centre for Cell Science (NCCS) in Pune and International Centre for Genetic Engineering and Biotechnology (ICGEB) in New Delhi.

Malaria is an important tropical parasitic disease. Relatively it kills more people than any other communicable diseases except, maybe, tuberculosis. In developing countries, especially in Africa, malaria leads to enormous loss of human lives and serious economic and medical costs. The causative agents in humans are four species of single-celled parasites, borne by mosquitoes. Among them the parasite, P. falciparum accounts for majority of the lethal infections. Now with the emergence of the multi drug resistant strains of parasite, the situation is being viewed with grave concern as malaria is again re-emerging in area where it was previously under control or eradicated, eg., in the central Asian Republics of Tajikistan and Azerbaijan and in Korea.

New lead molecules

In India, Dr Anil Chatterji along with his team had been working on this project since 2004. "During the first six months of the project itself we were able to identify and zero in on the lead compounds", said Dr Chatterji. The researchers found that the crude extract prepared by the enzymeâ€“acid hydrolyzing process from a marine organism (mussel) showed a potent anti-malarial activity initially, when examined for in vitro cultures of Plasmodium falciparum in human erythrocytes. This led to the isolation and characterization of the molecular entity (ies) responsible for anti-malarial activity, which involved activity guided fractionation strategy where a variety of chromatographic steps were employed. These included High Performance Liquid Chromatography (HPLC) using a range of columns (hydrophobic, selective absorption, ion exchange, etc.) preparative thin layer chromatography, selective derivatization and gel filtration chromatography. The scientists took care to monitor the selectively enrichment of activity at every step by using P. falciparum culture for in vitro studies. Eventually they identified two compounds that independently showed anti-malarial activity.

Now with the compounds successfully identified, the next step was to define the structure of the compounds. With the compound geometry in place the researchers validated the elucidated structures and found them to be potent. During their further studies, scientists found that the two lead compounds (named as NIO-1 and NIO-2) displayed biological activity against the malaria parasite both in mouse and human cells. Both the compounds exhibited activity against P. falciparum for in vitro culture assay.

A significant discovery during the studies on the action mechanism of the compounds was the fact that the compounds acted by directly killing parasite rather than just causing inhibition in their growth. This was coupled with the encouraging find that no effect of the drug was seen on the host cell in any of the experiments. This confirmed that the compounds are non-toxic and potentially very attractive as drug candidates. In addition, NIO-2 displayed activity against the chloroquine-resistant strain-W2Mef. This strongly suggested that the compound (NIO-2) would be equally effective against field isolates of chloroquine resistant, P. falciparum. The mechanism of action of NIO-2 on W2Mef strain was again by killing the target.

Although NIO-1 did not show any activity against the W2Mef strain, at least at the concentrations tested, but the scientists are not ruling out the possibility that it may act against field isolates of chloroquine-resistant strains. Nevertheless the researchers concur that NIO-1 provides an alternative to existing drugs in the field, and would serve to minimize chances of producing drug resistant variants in the field.

When both, NIO-1 and NIO-2, were tested in vivo in mice, they showed anti-malarial activity in consistence with the earlier results. Further, blood smears from drug treated mice also supported that the compounds act through killing the parasite in vivo.

Another encouraging find was that the bioactivity of NIO-2 is retained when delivered through the oral route, reemphasizing that it is a drug of high promise. Presently, the researchers are examining the oral mode of treatment for NIO-1 and it is expected to be completed shortly.

The molecules ideally suit the needs of the developing nations as the active compound of both these promising candidate drugs is relatively cheap to obtain and can readily be prepared in bulk without even killing the mussel. "Our aim is to develop a cost effective drug with high efficacy having no side effects. And going by the data generated by the pretoxicity trials the results look very optimistic and encouraging", shared Dr Chatterji. "After identifying the lead molecules, we took about a year to find a suitable company to give the licensing rights", he added. Mumbai-based Shreya Life Sciences has been licensed to commercialize the drug and the agreement is worth $0.4 million. Currently the preclinical toxicity trials are over and after a few more tests, the company will file the application with the Drug Controller General of India (DCGI) for conducting the clinical trials.

In view of the studies already done, the researchers opine that both NIO-1 and NIO-2 are promising candidate drugs for malaria and may be used in conjunction with conventional drugs.

Rolly Dureha