

Investigations on Natural Products Leading to Discovery of a Novel Biochemical Pathway

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Our groups have investigated several *Piper*, *Taxus*, *Prunus* and *Cephalotaxus* species and isolated a large number of novel compounds belonging to the classes of alkaloids, polyphenols, steroids, amides, terpenoids, etc. Many of them have shown interesting biological activities, remarkable of them has been our extensive work on polyphenol acetates leading to the discovery of a novel fundamental biochemical pathway involving acetyl CoA-independent enzymatic protein acetylation. Our seminal investigations have highlighted the unique biochemical and pharmacological actions of polyphenol acetates. We have discovered a novel membrane bound transacetylase enzyme which catalyses the transfer of acetyl groups from polyphenol acetates to certain receptor enzyme proteins, such as cytochrome P-450 linked mixed function oxidases (MFO), NADPH cytochrome c reductase and glutathione S-transferase (GST) resulting in modulation of their catalytic activities. The purified enzyme from buffalo liver in the presence of polyphenol acetates (PAs) catalyzed the acetylation of GST 3-3. The N-terminus and six other lysines (Lys-51, -82, -124, -181, -191 and -210) of GST 3-3 were found to be acetylated. TAase catalyzed the irreversible inhibition of P-450 enzymes and GST by PAs, while NADPH cytochrome c reductase was irreversibly activated. Polyphenol acetates were also found to significantly enhance the Nitric Oxide Synthase (NOS) activity in human platelets, possibly by way of TAase catalyzed acetylation of the reductase domain of NOS. PAs when incubated with platelets were found to profoundly inhibit ADP induced platelet aggregation. The deacetylated products of PAs were devoid of the ability to inhibit platelet aggregation, thereby implying the critical role of acetyl groups of PAs in TAase mediated modulation of enzymatic activities. These investigations project polyphenol acetates as promising drug candidates for enhancing the intracellular NO levels, which are of immense importance in various physiological events and in the control of several diseases. Details of these studies shall be presented at the ICNPAS-2004 and 3rd EAHM-2004 Conferences in Novosibirsk.