

levels of a drug. Various routes of administration are used in which, per-oral route is most preferred, being cost-effective and patient friendly. However per oral delivery presents many hurdles starting from drug dissolution in gastrointestinal (GIT) fluid to first pass metabolism and also due to various physicochemical and bio-pharmaceutical problems. With the result, oral therapy has limitations of large variability in the rate and extent of absorption of a therapeutic agent into the systemic circulation.

Maximizing bioavailability of an orally administered drug is therapeutically important because the extent of bioavailability directly influences plasma concentrations, as well as therapeutic and toxic outcomes. Poorly bioavailable drugs are inefficient because a major portion of a dose never reaches the plasma or exerts its pharmacological effect. The inter-subject variability in bioavailability also remains correlated with the extent of bioavailability. Therefore low bioavailability leads to high variability and poor control of plasma concentration and effects. Inter-subject variability is particularly of concern for a drug with a narrow therapeutic margin or a steep dose vs. effect profile [1].

Considerable evidence is accumulating to suggest that many clinically important anticancer drugs are not optimally utilized when taken orally. Majority of anticancer drugs show poor and variable bioavailability after their oral administration: many even with higher bioavailability show unpredictable variability [2, 3]. If systemic availability of a drug averages 20%, for example, then 80% of a dose is simply wasted. For drugs that are expensive to produce and beyond the reach of millions, wasting 80% of the precious substance is not comprehensible. There is, thus, a need to search for alternative drug forms having better action profile in terms of oral availability and efficacy.

Since the beginning of its clinical development 40 years ago, etoposide has remained an important and widely used agent in clinical oncology. Its integral role in the treatment of germ cell tumors and small-cell lung cancer seems unlikely to diminish in the future, and its use in non-Hodgkin's lymphoma and

in various high dose regimens will probably continue to increase. Etoposide can be given using i.v. and oral formulations. The i.v. dose ranges from 100 to 120 mg/m², whereas the oral dose ranges from 200 to 240 mg/m², reflecting the fact that etoposide has an oral bioavailability of ~50%. After oral administration, the absorption of etoposide is erratic and incomplete: both the rate and extent of absorption vary considerably among individuals, and even within the same individual, during chronic or multiple dosing, there is wide (25 - 80%) intra-patient and inter-patient variability in systemic exposure and clearance [2, 4-12].

Improving oral absorption and bioavailability of etoposide has therefore remained an important issue within the pharmaceutical industries. Investigation for newer active etoposide combination regimens continues for achieving improvement in its clinical activity with respect to its optimal dose and schedule.

In recent times a new dimension in chemotherapeutics is being witnessed with regard to the development of drug enhancing technologies which will have revolutionary shift in the way medicines are administered. The global focus therefore is on newer approaches to reduce the drug dosage (and consequently cost), making treatment more affordable to a larger section of the society, along with lesser toxicity concerns.

In this context *herb-herb* and *herb-drug* interactions have gained a major focus, with increasing trend towards the use and understanding of natural products as an alternative to the conventional treatment or as an additional medicine to boost the conventional therapy. A vast literature is now available with respect to important pharmacokinetic interactions of wide variety of natural products (or their analogues) primarily derived from reputed medicinal herbs which have shown that such interactions could produce potential effect in vivo, among which drug bioavailability is one important pharmacological consequence [13,14].

In the recent past considerable research has been going on at CSIR- Indian Institute of Integrative Medicine (I.I.I.M.), Jammu in order to identify and develop bioenhancers which could effectively enhance the bioavailability of clinically important drugs which show poor bioavailability after oral administration. In this regard multiple bioenhancer moieties derived from natural (herbal) sources as well as their analogues have been investigated. During the last decade concerted research efforts have resulted in identifying an active alkaloid molecule piperine (1-piperoyl piperidine) from piper species, and also some other natural substances which have shown to increase the bioavailability of a large number of drugs and pharmaceutical agents, and other pharmacologically active substances (phenytoin, propranolol, theophylline, nevirapine, beta-lactam antibiotics, curcumin, coenzyme Q10, and epigallocatechin) in animals and human volunteers. A vast amount of information on the role of piperine as bioenhancer has been documented in many published reports [15-22]. The mode of bioenhancer action of piperine has been understood in its ability to influence the intestinal permeability, and a potential CYP 3A4/ P-gp inhibitory role [23-25].

In a significant development, CSIR-I.I.I.M., Jammu in public - private partnership with Cadila Pharmaceutical Ltd, Ahmedabad, has released a new drug formulation against tuberculosis called '*risorine*', (containing a reduced dose of rifampicin along with isoniazid and piperine), which has been found to be bioequivalent to standard rifampicin regimen. Launched in November 2009, this indigenously developed drug formulation has been approved for marketing by Drug Controller General of India after successful completion of all the phased clinical trials.

Recently a novel series of substituted piperine analogues have been synthesized at CSIR- IIM, Jammu [26], and these analogues (including piperine) have been evaluated for identifying potential leads as enhancers of drug bioavailability with special emphasis on anti-cancer agents. During the preliminary investigations one such analogue namely, 4-ethyl 5-(3, 4-methylenedioxyphenyl)-2E, 4E-pentadienoic acid piperidide, (PA-1) (**Fig. 1**)

was found to be a promising entity as bioavailability enhancer for the drug etoposide.

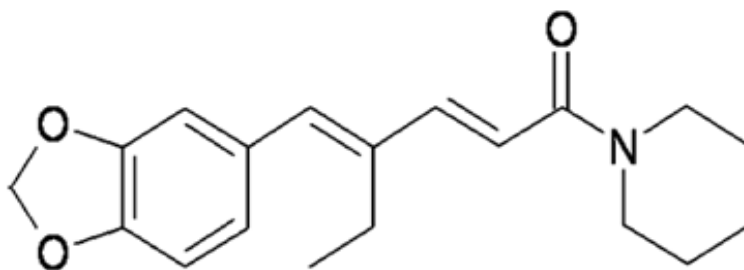


Fig. 1: 4-Ethyl 5-(3,4-methylenedioxyphenyl)-2E,4E-pentadienoic acid piperidine

The present study deals with a detailed investigation on the pharmacokinetic interaction of PA-1 with etoposide in mice, which has resulted in a significant enhancement of bioavailability of orally administered etoposide. A mechanistic evaluation has also been undertaken to examine the mode of action of PA-1 by studying some key biochemical events such as absorption/efflux, and metabolism of this drug, as influenced by P-glycoprotein (P-gp), and selected cytochrome P450 (CYP) enzymes, which are now recognized as major regulators of oral drug bioavailability.