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Herb-drug interaction of *Andrographis paniculata* (Nees) extract and andrographolide on pharmacokinetic and pharmacodynamic of naproxen in rats

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ABSTRACT

Ethnopharmacological relevance: *Andrographis paniculata Nees* (Acanthacae) have broad range of pharmacological effects such as hepatoprotective, antifertility, antimalarial, antidiabetic, suppression of various cancer cells and anti-inflammatory properties and is widely used medicinal plant in the traditional Unani and Ayurvedic medicinal systems. Andrographolide (AN) is one of the active constituent of the *A. paniculata Nees* extract (APE). They have been found in many traditional herbal formulations in India and proven to be effective as anti-inflammatory drug.

Aim of the study: To evaluate the pharmacokinetic and pharmacodynamic (anti arthritic) herb-drug interactions of *A. paniculata Nees* extract (APE) and pure andrographolide (AN) with naproxen (NP) after oral co-administration in wistar rats.

Materials and methods: After oral co-administration of APE (200 mg/Kg) and AN (60 mg/kg) with NP (7.5 mg/kg) in rats, drug concentrations in plasma were determined using HPLC method. The main pharmacokinetic parameters of C_{max}, t_{max}, $t_{1/2}$, MRT, Vd, CL, and AUC were calculated by non-compartment model. Change in paw volume, mechanical nociceptive threshold, mechanical hyperalgesia, histopathology and hematological parameters were evaluated to study antiarthritic activity.

Results: Co-administration of NP with APE and pure AN decreased systemic exposure level of NP in vivo. The C_{max}, $t_{max,}$ AUC_{0-t} of NP was decreased. In pharmacodynamic study, NP (10 mg/kg) alone and NP+AN (10+60 mg/kg) groups exhibited significant synergistic anti-arthritic activity as compared to groups NP+APE, APE and AN alone.

Conclusion: The results obtained from this study suggested that NP, APE and pure AN existed pharmacokinetic herb–drug interactions in rat which is correlated with anti-arthritic study. The knowledge regarding possible herb–drug interaction of NP might be helpful for physicians as well as patients using AP. So further studies should be done to understand the effect of other herbal ingredients of APE on NP as well as to predict the herb–drug interaction in humans.

1. Introduction

Naproxen (2-(6-methoxynaphthalen-2-yl) propionic acid) (NP, Fig. 1) belongs to class of NSAIDs, widely used in the treatment of rheumatoid arthritis for mild to moderate pain relief (Cicala et al., 2000). *Andrographis paniculata* Nees (AP) is a traditionally used medicinal plant in Korea, Thailand, China, Japan, South Africa, India, Pakistan and Srilanka for the treatment of fever, cold, inflammation,

Abbreviations: AN, Andrographolide; ANOVA, Analysis of variance; APE, *Andrographis paniculata Nees* Extract; $AUC_{0-\infty}$, Area under plasma concentration-time curve extrapolated to infinity; AUC_{0-t}, Area under plasma concentration-time curve from zero to last time point; $AUMC_{0-\infty}$, Area under the concentration time (c×t) versus time (t) curve for extrapolated to infinity; $AUMC_{0-t}$, Area under the concentration time (c×t) versus time (t) curve for last time point; CL, Plasma clearance; C_{max}, Peak plasma concentration; CV, Coefficient of variation; CYP, Cytochrome P450; DMARD, Disease-modifying antirheumatic drug; EDTA, Ethylenediaminetetra-acetic acid; HPLC, High performance liquid chromatography; I.S., Internal Standard; Ke, Elimination rate constant; $MRT_{0-\infty}$, Mean Residence Time extrapolated to infinity; MRT_{0-t}, Mean Residence Time from zero to *t* hours; NSAID, Non steroidal anti-inflammatory drug; NP, Naproxen; r, Correlation coefficient; SD, Standard deviation; SEM, Standard error of the meanl; $T_{½}$, Elimination half-life; Tmax, Time when Cmax occurs; Vd, Apparent volume of distribution

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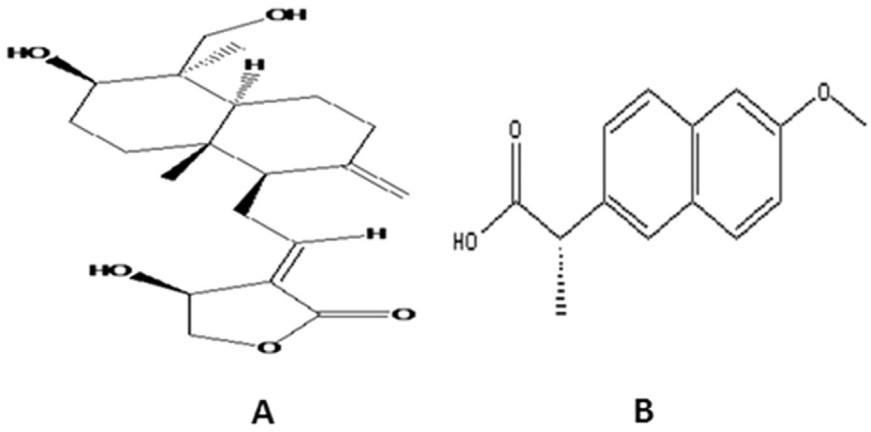

Fig. 1. Chemical structures of Andrographolide (A) and Naproxen (B).

diarrhea and other infectious diseases. Since 175 BCE, *A. paniculata* along with other plants in polyherbal preparations was recommended in Charak Samhita for treatment of jaundice. Indian pharmacopoeia mentioned that *A. Paniculata* is a predominant constituent of at least 26 Ayurvedic formulations. (Jarukamjorn and Nemoto, 2008; Ooi et al., 2011; Qui et al., 2012; Dhiman et al., 2012; Shen et al., 2013, Carretta et al., 2009). Andrographolide one of the major active components of the plant *A. paniculata* has been extensively used in traditional herbal medicine in China, Southeast Asia, and the Arabian Gulf for the treatment of several diseases, including inflammatory diseases. (Abu-Ghefreh et al., 2009). Traditional use of *A. Paniculata* as anti-inflammatory herb has been studied by various scientists and proved the mechanism (Hidalgo et al., 2005b; Abu-Ghefreh et al., 2009; Shen et al., 2013; Low et al., 2015). Inflammatory responses are critical part of the pathophysiology of several diseases, including septic shock, cancer, atherosclerosis, rheumatoid arthritis, and diabetes. So the manipulation of inflammatory responses may allow for the prevention of serious diseases or symptoms (Shen et al., 2013). The extracts of AP and its isolated compounds are also reported to have various pharmacological activities, including hepatoprotective (Visen et al., 1993), antidiabetic (Nugroho et al., 2013) inhibition of replication of the HIV virus (Uttekar et al., 2012), antimalarial (Mishra et al., 2011) and principally anti-inflammatory properties (Shen et al., 2013; Hidalgo et al., 2005b). Andrographolide (AN, Fig. 1) one of the active constituent of *A. paniculata Nees* has been reported to have anti arthritic effect. Production of pro-inflammatory mediators, such as COX-2, iNOS and cytokines has been reduced by AN (Carretta et al., 2009). In clinical trials, *A. paniculata* extract (30% AN) showed the effectiveness of symptom relief and reduce serological parameters in patients with Rheumatoid Arthritis (Hidalgo et al., 2005a).

Several polyherbal formulations consisting AP as a major ingredient as anti-inflammatory and anti-arthritic are available in local Indian markets. In treatment of arthritis, it is common practice that, along with the disease–modifying antirhumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs), herbal formulations are either taken with or without knowledge of health care provider by the patients for better therapeutic effects. This may lead to either beneficial or toxic effects. An increasing consumption of medicinal herbs, which are often administered in combination with conventional therapeutic drugs, it is likely that constituents in herbal preparations may be substrates, inhibitors, or inducers of cytochrome P450 enzymes (CYPs) and have an impact on the pharmacokinetics and pharmacodynamics of any co-administered drugs metabolized by this system (Zhou et al., 2003). Many studies have been reported for interaction between *A. paniculata Nees* extract and AN with various synthetic drugs (Chen et al., 2013; Chien et al., 2010). Recently we have reported the pharmacokinetic and pharmacodynamic interaction of APE and AN with Etoricoxib and Nabumetone (Balap et al., 2016a,b). Unfortunately, not a single attempt has been done to investigate the interaction of AP and it's one of the major constituent AN with NP after oral administration in rats. Previously various bioanalytical methods are reported in literature for the determination of andrographolide alone and in combination with other drugs (Panossian et al., 2000; Naidu et al., 2009). Seldom bioanalytical methods are previously reported in literature for the determination of NP in rats and humans (Josa et al., 2001; Aresta et al., 2005). However, there is no analytical method is available for simultaneous estimation of AN and NP. Prompted by the above findings, an attempt to develop a new validated HPLC method for simultaneous determination of AN and NP in rat plasma and application of the developed method for pharmacokinetic study in rats has been done. The aim of the present study was to investigate the possible herb-drug interactions of APE and AN with NP through comparing their pharmacokinetic profiles and pharmacodynamic after oral administration in rats.

2. Materials and methods

2.1. Chemicals and reagents

Naproxen was obtained as a gift sample from Cadila Healthcare Ltd. Ahmedabad and Carbamazepine (IS) was obtained as a generous gift from Emcure Pharmaceuticals Pvt. Ltd. Pune. HPLC grade Acetonitrile was purchased from Merck Chemicals, Mumbai, Maharashtra, India. Andrographolide (AN) was purchased from Research Organic Pvt. Ltd, Chennai. *A. paniculata Nees* extract (APE) was procured from Natural Remedies Pvt. Ltd, Bangalore (Batch No. FAPEX/2013110012). Phytochemical analysis performed by HPLC with stating ≈30% w/w andrographolide in the extract. High purity deionized water was obtained from Millipore, Milli-Q (Bedford, MA, USA) water purification system.

2.2. Animals

Female wistar rats weighing 180–220 g were purchased from National Institute of Biosciences. Six rats were placed in one cage, and maintained under controlled room temperature (25 ± 2 °C) and humidity (60–70%) with day/night cycle (12 h/12 h). All animals had free access to food and water. After acclimatization for 7 days animals were fasted overnight (12 h) prior to each experiment. All experiments were performed as per the guidelines of CPCSEA after obtaining approval (1703/PO1C/13/CPCSEA) from the Institutional Animal Ethics Committee.