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Andrographis paniculata Nees a well-known Hepatoprotective drug: A review

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Abstract
The plant *Andrographis paniculata* Nees is commonly called as king of bitters or Kalmegha. It has secondary metabolites like diterpene lactone andrographolide and andrographanine. The therapeutic efficacy is mainly because of the presence of these secondary metabolites. The wide range of pharmacological activities are exhibited by the extracts of this plant and the major use is seen in the hepatoprotective activity.

Keywords: *Andrographis paniculata*, kalmegha, folk ethnobotany, phytochemistry pharmacology

1. Introduction
Andrographis paniculata Nees (Acanthaceae) is one of the 19 species of the genus *Andrographis*, distributed in India, Pakistan and Srilanka. It normally grows in hot and shady places. It is also cultivated in certain parts of India, East and West Indies, Mauritius and also in China and Thailand. Based on the population decline, habitat destruction, other factors it is categorised under the threat status Lower risk [1].
Kannada: Nelabevu; Hindi: Kalmegh; Sanskrit: Bhunimba, Kiratatikta; Tamil: Nelavempu; Telugu: Nelavepu; English: Green Chiretta, Creat.

2. Description
It is an erect, branched, annual herb, 1-3' height; stem quadrangular; leaves simple, lanceolate, acute at both ends, glabrous, main nerves 4-6 pairs; flowers small pinkish white; calyx lobes glandular, pubescent; corolla bilipped with bluish pink colour; anthers bearded at the base; fruits linear capsules; seeds 8--10, wedge shaped, surface with faint reticulation, brownish yellow coloured[1].

3. Medicinal uses
It is commonly called as 'king of bitters' and whole plant and leaves are used as drug. It is used for various ailments. It has a bitter taste, acrid and cooling.
Charaka (900 B.C.) mentioned the use of *A. paniculata* to cure jaundice, as a galactodepurant and antidyspic [2,3]. Bhavamishra's (1550) treatise Bhavaprakasha indicates its use in Tridosha (Vata, Pitta, Kapha) [4]**.** It is used as antipyretic, anthelmintic, stomachic. It is useful in burning sensations, wounds, ulcers, chronic fevers, malarial fevers, inflammations, cough, bronchitis, diarrhoea and dysentery [5,6,7].
Alui an household medicine made of leaves of *A. paniculata* is used to treat children for stomachic problems and typhoid fever in Bengal [8]**.** It is also used to cure diabetes, skin diseases, to prevent loss of sense and to cure epilepsy.
It is used extensively in folk and ethnomedicine to cure dysentery, diarrhoea in cattle, fever and tuberculosis in human beings [1, 9.10, 11, 12,]
Two ayurvedic drugs: Kalmeghnamayas and Kalmeghashiva are prepared from *A. paniculata*. The churnas such as Katu churna and Swetradiphala churna contain *A. paniculata* as one of the ingredients.
In China brew is prepared from *A. paniculata* and also Bengal Pharmaceutical Works Ltd., Bengal, prepares a brew from *Andrographis paniculata* for commercial purposes [9]. *Andrographis paniculata* is used in 26 different formulations of the various pharmaceutical industries [13] *Andrographis paniculata* is used as a substitute for *Swertia chirayita* (Gentianaceae) a potent hepatoprotector and widely used herbal drug. The most common adulterants to *Andrographis paniculata* are *Indoneesiella echioides* (Acanthaceae) and *Solanum indicum* (Solanaceae).

4. Ethnomedicinal value of *A. paniculata*
A. *paniculata* Nees is a very important medicinal plants being used by various ethnic groups to cure ailments of human as well as cattles and other domestic animals in India and other parts of the world. The available literature reveals that the whole plant extract with hot water is used orally in mild cases of malaria, for diabetes and for fevers in peninsular region of Malaysia [14]. The decoction of dried whole plant of *A. paniculata* is used orally for malaria, along with jaggery and it is used as an appetizer by chenchu tribe of Andhra Pradesh. *Andrographis paniculata* powder is mixed with garlic and 3 g is given orally with butter milk twice daily for four days in folk medicine of Chittoor district to cure acute jaundice [14]. Its hot water extract is given orally to human adult to cure dyspepsia, dysentery and for debility [15]. The study on Kani tribe of Trivendrum listed as many as 100 drugs [16]. *A. paniculata* is one among them and which is used for anemia, as an appetizer for children and it is made in to decoction with dried ginger and *Ocimum sanctum* to cure malaria. The use of this plant for dyspepsia, dysentery and debility in Kamrup

district of Assam [17]. The use of this plant for fever, dysentery, dyspepsia and to treat worms by using hot water extract orally. It is also used for liver disorder and the plant is powdered in sarson oil and used externally to stop itching [18]. Equal quantities of *A. paniculata*, *Azadirachta indica* and *Holarrhena antidysenterica* are pounded, mixed with 6 volumes of water and heated with a hot brick, 25 ml of infusion is taken orally 3-4 times a day for 3 days to cure jaundice [18]. Hot water extract of leaf of *A paniculata* is given orally as anthelmintic and febrifuge [20, 21]. The dried leaf extract is used subcutaneously in human adult for filariasis [14, 22]. The leaves of *A. paniculata*, *Tinospora cordifolia* and *Solanum surattense* are taken for 5 days for fever and water extract of dried leaf of *A. paniculata* is used orally as febrifuge, as tonic and as an anthelmintic. The review on ethnomedicine of Thailand mentioned the use of leaf decoction in the treatment of high blood pressure [23]. The use of fresh leaves of *A. paniculata* as an antidote for snake venom, where-as poultice of fresh leaves is applied to the affected area [24]. The water extract of leaf and stem is used orally as powerful tonic and as a substitute for quinine [25]

5. Phytochemical studies

An attempt to isolate the active principle and obtained a colourless neutral substance, which he called as andrographide [26]. Gorter (1911) isolated a bitter principle in pure crystalline form a lactone, with a molecular formula $C_{20}H_{30}O_5$ and changed the name to andrographolide which is in use today. Researchers isolated a new lactone neoandrographolide from *A. paniculata*, and deduced the molecular formula $C_{23}H_{38}O_8$ with α, β, γ (unsaturated) lactone having the melting point 157^0C [27]. The positive legal test was observed and the UV absorption maxima (λ max) was observed at 223 nm. Also α-β-unsaturated lactone, homoandrographolide, a sterol andrographosterol, a hydrocarbon, panicula wax and 2 different esters containing -OH groups from petroleum ether extract are isolated [28]. The root extracted with acetone yielded a new flavone, 5-hydroxy-7,8,2',3'-tetramethoxy flavone when eluted with benzene [29]. The structure of two diterpenoid glucosides is elucidated from the more polar fractions of plant extract [30]. A diterpenoid glucoside, deoxyandrographolide-19-β-D-glucoside with m.p. 201^0C and UV λ max 205 nm (in methanol) isolated from the leaves of *A. paniculata* Nees. [31]. 2 new flavonoids are isolated and characterized by subjecting petrol extract to column chromatography [32]. Crystallographic analysis by X-ray diffraction has reported the absolute configuration of andrographolide which was previously not known [33]. The modified gravimetric method for estimation of andrographolide was described in Kalmegh [34]. It is proposed that the colorimetric method for estimation of andrographolide where the red colour obtained after the addition of alcoholic potassium hydroxide to the andrographolide is measured [35]. further unsatisfied with the method of Maiti *et al.*, (1959) suggested a chemical method involving lactone titration to group andrographolide as a lactone [36]. The spectrophotometric method was used to obtain the characteristic peak at 226 nm indicating the presence of andrographolide in methanolic solution, was proposed [37]. The improved titrimetric estimation of andrographolide involved background correction due to the presence of impurities was suggested [38]. A rapid method for quantifying andrographolide by TLC in aqueous alcoholic extract of leaves of *A. paniculata* [39].

6. Pharmacological activity of *Andrographis paniculata*

A Hepatoprotective activity

The characteristic inhibition in hepatic microsomal anilinehydroxylase, N-demethylase and O-demethylase after several times of treatment of both Kalmegh leaf extract and Andrographolide at the dose of 0.5, 1, 5 and 10 mg/kg body weight orally to male albino rats [40]. It was also observed that more pronounced effect in Kalmegh then of Andrographolide. When the comparative efficacy of Liv. 52 and *Andrographis paniculata* was studied on CCl_4 induced hepato toxicity, Liv. 52 have shown good activity compared to *A. paniculata* in restoration of liver function and in these generative changes of liver [41]. The efficacy of aqueous extract of *A. paniculata* in liver damage in experimental rats, the significant liver protective activity was observed in this study [42]. A promising anti HBSAg like activity in picroliv which contains *A. paniculata* as one of the component [43]. Hepato-protective activity in two different models viz Galactosamine and paracetamol induced intoxication, in both the models Andrographolide, the active constituent of *A. paniculata* at the dose 400 mg/kg ip 800 mg/kg oral significantly protected the liver damage in rats. They have also studied significant hepatoprotective activity of andrographolide obtained from *A. paniculata* against carbon tetrachloride induced hepato toxicity. Further 100 mg/kg ip off andrographolide normalizes the CCl_4 induced hepatotoxicity by increasing the bile flow and by lowering weight and reduces hexapentobarbitol induced sleeping time in mice [44]. Alcoholic extract of leaves of *A. paniculata* obtained by cold maceration at the dose of 300 mg/kg was found to be effective against CCl_4 induced liver damage which was evident by the results of biochemical, morphological and functional parameters [45]. The antihepatotoxic activity of some of the plants like *A. paniculata, Eclipta alba, Plumbago zeylanica* and *Tephrosia purpuria* ingradients of herbal formulation but, *A. paniculata* and *T. purpurea* were found to be most active ones [14, 46]. The effect of hepatogard an herbal preparation against CCl_4 induced liver damage, they found the beneficial activity of the herbal formulation including drugs such as *Picrorrhiza kurroa*, *Andrographis paniculata*, *Phyllanthus amara*, *Boerhavia diffusa*, *Azadirachta indica*, *Triphala*, *Eclipta alba*, *Zingiber officinalis* and *Piper longum* [46]. Work on *A. paniculata* and *Phyllanthus emblica* for their action against viral hepatitis using 500 mg tablet made out of both ingredients for 2-3 months in patients observed effective and safe drug on viral hepatitis [47]. An herbal drug containing six plants including *A. paniculata* was evaluated in patients of cirrhosis, the extent of improvement by the drug was determined by estimating serum antipyrin half life. This drug significantly reduced antipyrin half life. Even pre-treatment of this drug is effective in inhibiting triglyceraldehyde accumulation in hepatic cells in CCl_4 induced chronic and acute liver damage in rats [48]. Evaluation of the hepatoprotective activity of andrographolide isolated from *A.*

paniculata in conscious rats as well as anaesthetised guinea pigs. The andrographolide is found to be very potent than Silymarin, a known hepato protective drug [49]. **T**he paracetamol induced hepatopathy in sheep using two herbal preparation starting from 1st day to 10th day. The treatment to animals showed that more effective in treating such cases [50].
In a review researchers have listed the plants used as hepato protective agents one such plants is *Andrographis paniculata* [51]. The combination of picroliv and andrographolide isolated from *Picrorrhiza kurroa* and *A. paniculata* respectively were found to be more effective as it showed choleretic, anticholestatic and hepato protective activity in rats and guinea pigs [49]**.**

B Antidiarrhoeal activity
The antidiarrhoeal activity of alcoholic extract of *A. paniculata* and 4 diterpenes obtained from n-butanol fraction against *Escherichia coli* enterotoxin in *in vivo* models [52]. The activity was found to be similar as that of standard drug Loperamide. Out of 31 plants screened for antidiarrhoeal activity against *E. coli* enterotoxin induced secretion in rabbit and guinea pig, only 5 plants viz., *A. paniculata, Cassia fistula, Colium forsklaei, Tridax procumbens* and *Papaver somniferum* showed highly significant anti diarrhoeal activity [53].

C. Immunostimulant activity
Humoral immune response stimulation and cellular immune response supression was observed when water soluble extracts of leaves of *Piper betle*, rhizome of *Zingiber aromaticum*, whole plant of *A. paniculata*, bulbs of *Allium sativum* and leaves of *Oldenlandia corymbosa* of the Indonesian plants administered intraperitonially and orally [54]. The work on *A. paniculata* using ethanolic extract and purified diterpene andrographolide induced significant stimulation of antibody and delated response of hypersensitivity (DTH) in sheep red blood cells (SRBC) in mice, the substances other than andrographolide present in the extract may also be contributing as immunostimulant agents [55].

D. Antipyretic activity
The study revealed the significant antipyretic activity of *Andrographis paniculata, Tinospora cordifolia* and *Solanum surattense* on experimental rats [16]. The effect of andrographolide isolated from *A. paniculata* in yeast induced pyrexia in rats and observed very good antipyretic activity[55],.

E. Antiulcerogenic activity
The significant antiulcerogenic activity of andrographolide is observed when administered to aspirin induced ulceration in rats [56].

F Cardiac diseases
Administration (iv) of flavone extract from roots of *A. paniculata* exhibited antithrombotic effect by preventing the formation of thrombi as well as the development of myocardial infarction in dogs [57]. The prevention of atherosclerotic arterial stenosis and restenosis after angioplasty in *Andrographis paniculata* was observed in rabbits, than fish oil [58].

G. Myeolid leukaemia
The study on mouse myeolid leukaemia (Ml) highlighted the potent cell differentiation inducing activity in methanolic extract and other diterpene compounds isolated from *A. paniculata* [59].

H. Antisnake venom property (Antidote)
The plants having folk claims with antisnake venom properties, *A. paniculata* is one among them and they have also conducted pharmacological and clinical studies of various plant extracts and their active principles against different snake venoms [60].

I. Antifertility activity
Andrographolide administered orally to male rats for 45 days at the dose of 10 mg/day has shown good antifertility activity [61]. **T**he antifertility studies in male albino rats fed with 20 mg/day of root powder of *A. paniculata* for 60 days by its anti spermatogenic and antiandrogenic effects [62]

J. Analgesic activity
The effect of andrographolide isolated from *A. paniculata* on analgesic activity, where the compound showed significant activity in acetic acid induced writhing movements and Randall selitto test in rats but did not show any activity in hot plate method[57],.

K. Antiprotozoal activity
Andrographis paniculata a known hepatoprotective and hepatostimulative agent was studied for its antimalarial activity against *Plasmodium berghii* NK 65 in Mastomys natalensis, a crude ethanol extract and fractions reduced the level of parasitaemia in dose dependent manner.

L. In Hair care
Reappearance of contour and texture was observed when ayurvedic drug containing *A. paniculata* as one of the ingredients against *Alopecia areata* (loss of Scalp hair) in both males and females of age group 10-45 years[64].

M. Hypoglycemic activity
Leaf and stem extracts of *A. paniculata* did not show any activity on blood sugar level of normal and diabetic rats [65]**.** The hypoglycemic activity of aqueous extract of *A. paniculata* against anaesthetised rats, but the lowering of blood sugar level during 7 hrs of study was absent in both orally treated and intraperitonially treated groups. However, the rat gut technique adopted to study the glucose absorption indicated the decrease in blood glucose level and demonstrated glucose tolerance test [65].

N. Anthelmintic activity
Study on 45 indigenous plants against human parasitic nematode *Ascaris lumbricoides* observed the significant anthelmintic activity of alcoholic extract of *Andrographis paniculata*, along with 11 more plants [65].

O. Anti-inflammatory activity
Aqueous extract of *A. paniculata* at the dose of 20 mg/kg body weight orally inhibited the oedema by 65.3% after 3 hrs as compared to the control group of rats.

P. Antimicrobial activity

The available literature has shown that *Andrographis paniculata* Nees has no antibacterial activity as evidenced by direct assay method, blood serum of healthy individuals by Agar diffusion method.

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