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Perspective of *Andrographis paniculata* in Neurological Disorders

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Abstract

Andrographis paniculata (Burm. F.) Wall. Ex Nees (Acanthaceae) is a labdane diterpinoids rich medicinal plant. Andrographolide is quantitatively the major bioactive secondary metabolite present in this herb. In Ayurveda, *Andrographis paniculata* is classified as a *Rasayana* herb. Several pre-clinical and well-controlled clinical trials performed during recent years have confirmed the therapeutic efficacies and broad safety profile of *Andrographis paniculata* as well as its secondary metabolites. Therefore, *Andrographis paniculata* seems to be another example of medicinal Ayurvedic plants which could not only be better explored for discovering structurally and functionally novel therapeutic leads, but also for identifying novel pharmacological principles and targets potentially useful for neurological disorders.

Keywords: *Andrographis paniculata*; Neurological disorders

Andrographis paniculata (Burm. F.) Wall. Ex Nees (family Acanthaceae) also known as *Kalmegh* (Figure 1), is extremely bitter in taste and it is often referred to as the "the king of bitters". This plant has been used as bitter tonic, stimulant, and aperients in Ayurvedic and other traditionally known health care systems widely practiced in India and other Asiatic countries. Amongst numerous plants of the *Andrographis* genus, *Andrographis paniculata* is the only one widely used for medicinal purposes, and it is also pre-clinically and clinically the most well studied one. Andrographolide (Figure 2) is quantitatively the major bioactive secondary metabolite of the plant [1], and it is now often considered to be a structurally and functionally novel therapeutic lead potentially useful for treatments for inflammatory diseases and cancer [2-9]. However, diverse types of medicinally used *Andrographis paniculata* extracts contain other structurally analogous labdane diterpenoids, oxygenated flavonoids, and numerous other bioactive secondary plant metabolites. Some of the major medical conditions commonly treated with such extracts is diabetes, liver disorders, common cold, dyspepsia and other diseases of the gastrointestinal tract [10]. Therapeutic efficacies in pre-clinical and clinical settings are summarized in Figure 3.

Figure 1: *Andrographis paniculata* (Burm. F.), a medicinal plant taxonomically classified as: Kingdom- Plantae; Order- Personales; Division- Angiosperma; Class- Dicotyledonae; Family- Acanthaceae; Genus- *Andrographis*, and Species- *paniculata*.

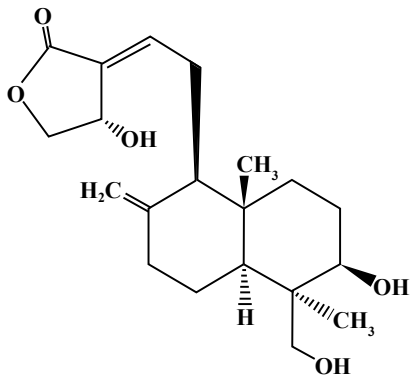

Figure 2: Chemical structure of Andrographolide.

The WHO monograph on *Andrographis paniculata* published during 2003 mentioned that its uses for prophylaxis and symptomatic treatments of upper respiratory tract infections, bronchitis, pharyngotonsillitis, lower urinary tract infections and acute diarrhea are supported by clinical data [11]. Since then several other clinical trials have not only continued to reaffirm such therapeutic benefits of diverse types of extracts of the plant, but also their therapeutic potentials for treatments of other diseases like rheumatoid arthritis [7,12], type-2 diabetes [13], and inflammatory bowel disease [14]. Several recent reviews summarizing currently available information on medicinal phytochemistry and pre-clinical and clinical pharmacology on *Andrographis paniculata* have appeared during recent years

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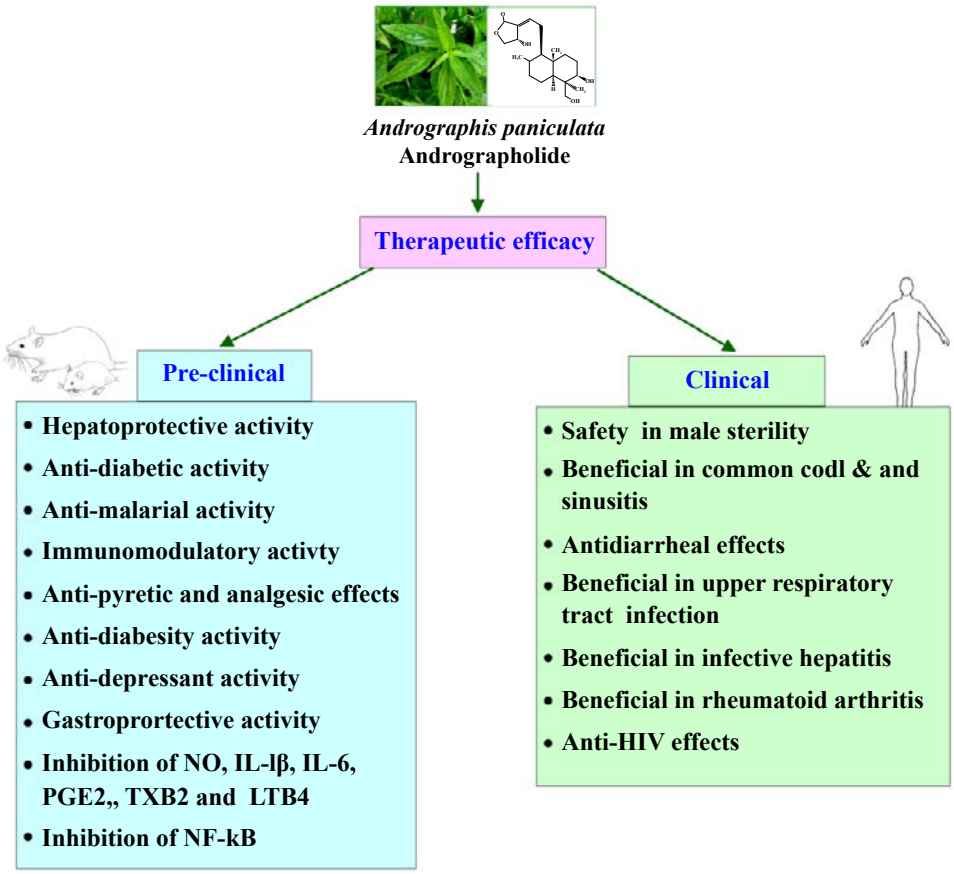

Figure 3: Therapeutic efficacies of *Andrographis paniculata* and Andrographolide.

[6,15,16]. Although as yet comparatively little attention have been paid to neuropsychopharmacology of andrographolide and *Andrographis paniculata*, recent preclinical observations made in our laboratories and elsewhere strongly suggest that they could as well be promising therapeutic leads potentially useful for prevention and cure of psychopathologies commonly associated with diabesity and diverse other chronic diseases with central sensitivity syndromes.

Comorbidities of depression and anxiety are often encountered in patients suffering from, or prone to, diabetes [17], and central sensitivity syndromes [18,19] almost always accompany all medical conditions for which traditionally known medicinal uses of *Andrographis paniculata* extracts are known since centuries. However, till recently only two preclinical reports on psychopharmacology of *Andrographis paniculata* extracts [20,21] and one patent on potential uses of andrographolide against neurological disorders had appeared [22]. However, the possibility that *Andrographis paniculata* extracts possess anti-stress or adaptogenic properties have often been pointed out by several modern scholars and researchers of traditionally known herbal remedies [23-27]. That such is indeed the case is reconfirmed by several recent observations made in our laboratories [28,29]. They clearly revealed that like many other herbal adaptogens, the therapeutically interesting antidepressants and anxiolytics like and stress response desensitizing effects of *Andrographis paniculata* extracts in animal models become detectable, or more prominent, after their daily oral doses only.

Although a vast majority of preclinical reports on such extracts, or on pure andrographolide, have dealt mainly with their therapeutically interesting bioactivities observed *in vitro* in cellular and other bioassay, or after their fairly high acute doses administered intraperitoneally or intravenously experimental animals, several reports on their therapeutically interesting pharmacological activities after their fairly low daily oral doses have appeared also. For example, it has been reported that fairly low daily oral doses (less than 10 mg/kg/day) of andrographolide or of *Andrographolide paniculata* extracts possess cardio-protective, antidiabetic and antihyperlipidemic and gastro- and hepato-protective activities in experimental animals [30-34], Several oral bioavailability studies conducted in experimental animals and volunteers have reaffirmed though, that very low, or undetectable, blood levels of andrographolide are observed even after it extremely high oral doses administered as pure compound or with *Andrographis paniculata* extracts [35-39]. Although several other authors reporting neuro- or cerebro-protective of andrographolide in *ex vivo* or *in vitro* experimental models have often also suggested that andrographolide could as well cross the blood brain barrier [40-44], it cannot be ignored that its biological half life is short and its blood levels are much lower than those necessary for observing its neuro-protective activity in cellular models.

In any case, available information on bioavailability of andrographolide and several other bioactive constituents of *Andrographolide paniculata* extracts clearly reveal that more than 95% of their orally administered doses are extensively bio-transformed within the gastrointestinal tract [35-37], and that if orally absorbed andrographolide can alter diverse drug metabolizing activities in liver and other peripheral organs [45-49]. Therefore, it seems

reasonable to assume that primary pharmacological targets involved in observed therapeutically interesting psychopharmacological and other bioactivities of pure andrographolide, or of diverse types of *Andrographis paniculata* extracts observed after their lower oral doses must resides inside the gastro-intestinal tract and in other peripheral organs. Consequently, it is apparent that their sites and modes of actions must be unlike those of most other known psychoactive drugs and therapeutic leads.

It is now well recognized that gut microbial ecology and the so called microbiota-gut-brain axis are involved in physiological regulation of brain functions and almost all metabolic processes [19,50,51]. Since andrographolide and numerous other well-known bioactive constituents of *Andrographis paniculata* extracts possess bactericidal, bacteriostatic, antiparasitic, and anti-viral properties [52] it can be expected that after their regular oral intake gut microbial ecology is altered, and as a consequence diverse metabolic processes, immunological functions of the gastrointestinal tract, and central sensitivity to metabolic and other sensory signals are also altered. Since andrographolide and other bitter tasting molecules present in *Andrographis paniculata* extracts are ligands of G-protein coupled bitter taste receptors, and existence and diverse functions of such receptors as chemo-sensors inside the gastrointestinal tract and other peripheral organs are now apparent [53-57], they could as well be their primary pharmacological targets. Moreover, it is known also that andrographolide forms covalent bonds with endogenous thiols and macromolecules involved in regulation of oxidative and inflammatory processes [58]. Therefore, it can be expected that the longer lasting and therapeutically interesting bioactivities of andrographolide observed in experimental animals after its oral administrations is due to its irreversible interactions with biologically important macromolecules within the gastrointestinal tract.

Therapeutically interesting preclinical information on medicinal phytochemistry and pharmacology of *Andrographis paniculata* extracts and andrographolide summarized in this communication strongly suggest that they are promising therapeutic leads potentially useful for treatments of diverse spectrums of psychopathologies commonly encountered in almost all lifestyle associated chronic diseases. Since their high efficacy and broad safety profiles have already been demonstrated [59-62], appropriately controlled and properly designed clinical trials necessary for firmly establish their psychotherapeutic potentials seems warrantable. Such efforts should eventually not only be useful for identifying validated novel pharmacological targets urgently needed for discovery and development drugs against neurological disorders of the 21st century, but also for better understanding of biological principles and processes involved in traditionally known widespread medicinal and health care uses of *Andrographis paniculata.*

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