Original Research Article

Pharmacological Activities of the *Andrographis paniculata* aka Nelabevu/Bhunimba

Abstract

Andrographis paniculata, commonly known as Nelabevu, Bhunimba, Chirayetah, Kalmegh, or Creat, is a plant with extensive traditional use in Asian medicines. Its historical application, particularly in conditions related to blood irregularities, has driven contemporary scientific investigations into its therapeutic potential. This review summarizes the diverse aspects of Andrographis paniculata's traditional uses and modern applications, covering its effectiveness in respiratory infections, hepatoprotection, cardiovascular effects, antimicrobial and anti-inflammatory activities, hypoglycemic effects, and reproductive influences. The plant's active constituents, such as andrographolide, flavonoids, and diterpenoids, contribute to its pharmacological actions. However, critical evaluation and further research are essential to confirm its clinical benefits and mechanisms of action. The extensive range of its effects and the multiple active compounds highlight the plant's significance in modern herbal medicine and warrant continued exploration.

Keywords

Andrographis paniculata, Nelabevu, Bhunimba, traditional medicine, ayurvedic medicine, antibacterial, antifungal, antiviral, reproductive effects, phytoconstituents, flavonoids, clinical trials, herbal medicine.

Introduction

Andrographis paniculata, a botanical treasure entrenched in the annals of traditional Asian medicine, has seamlessly transcended time to serve as a cornerstone of healing practices for generations. Its unique attribute of "blood purification" has rendered it indispensable in the management of diseases where blood irregularities are implicated as underlying factors, including afflictions such as skin eruptions, boils, scabies, and persistent undetermined fevers. The aerial components of this plant, harnessed for medicinal purposes, are a repository of a rich assembly of chemical constituents, prominently encompassing lactones, diterpenoids, diterpene glycosides, flavonoids, and flavonoid glycosides. Rigorous controlled clinical trials bear witness to its secure and efficacious role in mitigating symptoms of uncomplicated upper respiratory tract infections.

Nestled within the backdrop of traditional medical systems, where numerous disease conditions addressed by A. paniculata are inherently self-limiting, the proclaimed benefits of this botanical warrant a judicious and meticulous assessment. This review meticulously encapsulates the prevailing scientific revelations, underscoring the necessity for in-depth exploration to validate the therapeutic efficacy of A. paniculata.

A. paniculata, hailed as "Chirayetah" and "Kalmegh" in the linguistic tapestry of Urdu and Hindi on the Indian subcontinent, emerges as an annual botanical luminary, rising to heights of 1 to 3 feet. A stalwart within the traditional realms of Unani and Ayurvedic medicines, it assumes the English moniker "Creat" while proudly donning the title "king of bitters." Its presence graces the plains of India, adorning hedge rows and finding solace in cultivated gardens [1,2]. It stretches its roots beyond national boundaries, flourishing across various Asian nations where it is revered as a quintessential traditional herbal remedy. From China to Hong Kong, the Philippines to Malaysia, Indonesia to Thailand, its influence is profound.

While the aerial facets of the plant claim paramount utilization, select manuscripts allude to the incorporation of the entire plant or its roots for specific therapeutic intents. Its historical application spanned various forms - infusion, decoction, or powder, either singularly or synergistically amalgamated with other medicinal flora. In the contemporary milieu, a shift is discernible, as commercial preparations gravitate toward standardized whole-plant extracts, reflecting a convergence of tradition and modernity.

Amid the canvas of ailments traditionally assuaged by A. paniculata, the prevalent acknowledgment of their inherent self-limiting nature necessitates a discerning perspective on the proclaimed advantages. This synthesis adeptly distills the extant scientific tapestry while casting illumination on avenues that beckon further investigation [3,4]. The numbers referenced underscore the foundation of knowledge, guiding the voyage of understanding as we traverse the healing journey woven by Andrographis paniculata.

Traditional Applications of Andrographis paniculata in Medicine

A. paniculata has been documented to possess a range of beneficial effects, including antibacterial, antifungal, antiviral, choleretic, hypoglycemic, hypocholesterolemic, and adaptogenic properties [3]. Within the Unani medical tradition, it holds a significant place as it is regarded as aperient, anti-inflammatory, emollient, astringent, diuretic, emmenagogue, gastric and liver tonic, carminative, antihelmintic, and antipyretic. Its capacity for "blood purifying" makes it a recommended choice for addressing conditions such as leprosy, gonorrhea, scabies, boils, skin eruptions, and chronic as well as seasonal fevers [1]. For infants, a juice or infusion of fresh leaves is administered to alleviate griping, irregular bowel habits, and loss of appetite. Additionally, the leaves and roots find use in managing general debility during post-fever recovery, dyspepsia accompanied by gaseous distension, and advanced stages of dysentery [2,4,5].

In the context of Chinese medicine, the herb derived from A. paniculata's leaves or aerial parts goes by names like Chuanxinlian, Yijianxi, and Lanhelian. It is characterized as having a bitter and cold nature, acknowledged for its antipyretic, detoxifying, anti-inflammatory, and detumescent qualities. Its role involves dispelling "pathogenic heat" from the blood. A. paniculata is harnessed to treat various ailments including pharyngolaryngitis, diarrhea, dysentery, coughs with thick sputum, carbuncles, sores, and snakebites [6]. Diverse preparations and compound formulas of this herb have been employed to address both infectious and non-infectious diseases, showcasing notable efficacy rates for conditions such as epidemic encephalitis B, suppurative otitis media, neonatal subcutaneous annular ulcers, vaginitis, cervical erosion, pelvic inflammation, herpes zoster, chickenpox, mumps, neurodermatitis, eczema, and burns [6].

Modern Uses

A fundamental contemporary application of A. paniculata revolves around its utilization in both preventing and treating the common cold. Notably, its antithrombotic actions point towards a potential advantage in addressing cardiovascular ailments [7]. Through extensive pharmacological and clinical investigations, promising prospects have emerged regarding its efficacy in conditions such as cancer [8-12] and HIV infections [13].

Phytoconstituents Composition

Within A. paniculata, a variety of phytoconstituents can be identified. These include diterpenes, lactones, and flavonoids. Notably, flavonoids are predominantly found in the roots, although they have also been isolated from the leaves. The aerial parts of the plant contain compounds such as alkanes, ketones, and aldehydes. Initially, the belief was that the bitterness in the leaves stemmed from the lactone andrographolide. However, subsequent investigations unveiled the presence of two bitter components – andrographolide and a compound named kalmeghin. In China, four lactones named chuanxinlian A (deoxyandrographolide), B (andrographolide), C (neoandrographolide), and D (14-deoxy-11, 12-didehydroandrographolide) were extracted from the aerial parts [6].

Furthermore, the leaves have revealed the presence of a diterpene glucoside (deoxyandrographolide 19beta-D-glucoside), along with six ent-labdane type diterpenoids, two diterpene glucosides, and four diterpene dimers (bis-andrographolides A, B, C, and D). The whole plant yielded two identified flavonoids: 5,7,2’,3’-tetramethoxyflavanone and 5-hydroxy-7,2’,3’-trimethoxyflavone. Moreover, recent explorations have led to the discovery of 12 new flavonoids and 14 diterpenoids in the aerial parts. Additional novelties include two new flavonoid glycosides, a new diterpenoid known as andrographic acid, and two new ent-labdane diterpenoid glycosides isolated from the aerial parts [17-20].

Mechanisms of Operation

Hepatoprotective Effects

Andrographis paniculata, commonly known as A. paniculata, is widely employed as both a hepatostimulant and a hepatoprotective agent in Indian traditional medicine systems[21]. It serves as a vital ingredient in several polyherbal formulations utilized for their hepatoprotective properties in India[22]. Notably, one of these formulations has exhibited effectiveness against chronic hepatitis B virus infection[23]. Although there is limited research focusing on the impact of crude extracts of A. paniculata on liver function, the majority of studies concerning hepatic effects have been centered around andrographolide, the primary active compound of the plant.

Researchers have highlighted the significant choleretic effects of andrographolide. Studies conducted on conscious rats and anesthetized guinea pigs demonstrated that andrographolide provided superior protection against acetaminophen-induced reduction in bile volume and content compared to silymarin[24]. Additionally, the combination of arabinogalactan proteins and andrographolide administered in multiple doses exhibited hepatoprotective effects against ethanol-induced hepatotoxicity in mice, comparable to the efficacy of silymarin[25].

Further investigations revealed that administering an A. paniculata extract to adult rats, both before and after ethanol treatment, offered protection against the ethanol-induced elevation of serum transaminases. However, repeated single and multiple doses of the extract did not significantly affect serum transaminase levels in normal adult rats[26]. Comparing the effects of leaf extract and andrographolide on carbon tetrachloride (CCl4)-induced hepatic microsomal lipid peroxidation indicated a protective effect from a single oral dose of the extract and andrographolide. Interestingly, in vitro tests demonstrated that the extract entirely safeguarded against high-concentration CCl4-induced microsomal lipid peroxidation, whereas andrographolide alone did not, implying that the hepatoprotective effect is not solely attributed to andrographolide's presence[27]. Additional studies reported the hepatoprotective effects of crude alcohol extracts from the leaves against CCl4-induced liver damage[28].

Comparative studies by Handa and Sharma demonstrated that andrographolide, methanol extract of the entire plant (containing equivalent amounts of andrographolide), and andrographolide-free methanol extract exhibited inhibition of CCl4-induced liver damage in rats. This inhibition was evidenced by reduced levels of serum transaminases, serum alkaline phosphatase, serum bilirubin, and hepatic triglycerides by 48.6%, 32%, and 15%, respectively. Notably, all three treatments led to improved liver histology, suggesting that A. paniculata's constituents, beyond andrographolide, play a hepatoprotective role[29].

Moreover, andrographolide normalized the CCl4-induced increase in pentobarbitone-induced sleep time in mice. In comparison to other diterpenes, andrographolide exhibited protective effects against CCl4- or tert-butyl hydroperoxide-induced hepatotoxicity in mice, although compounds like andrographiside and neoandrographolide displayed even greater

protective effects. The protection conferred by andrographiside and neoandrographolide was comparable to that of silymarin, with neoandrographolide also normalizing glutathione levels[30].

Trivedi et al. observed that both the crude extract of A. paniculata and andrographolide offered protection against reduced activities of hepatic antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase), depletion of hepatic glutathione, increased activities of hepatic γ-glutamyl transpeptidase, glutathione-S-transferase, and lipid peroxidase, all of which were induced by hexachlorocyclohexane in mice[31]. Andrographolide, whether administered orally or intraperitoneally, was found to protect against galactosamine-induced liver damage in rats. This protective effect extended to preventing changes in biochemical parameters and liver histology, even when andrographolide was administered post-acetaminophen challenge. Similar protective effects were also observed in an ex vivo preparation of isolated rat hepatocytes[32-33].

The experiments mentioned in this section employed various extracts and components of A. paniculata, all of which demonstrated hepatoprotective effects. Furthermore, A. paniculata showcased its efficacy against liver damage induced by agents with different hepatotoxic mechanisms, suggesting that both A. paniculata and its constituents possess broad-spectrum hepatoprotective effects. However, more research is necessary to ascertain the most effective component(s) for hepatoprotection. The establishment of this component's identity warrants large-scale, multicenter clinical studies to determine the efficacy of A. paniculata in treating liver diseases of diverse origins[21-33].

Influence on Hepatic Metabolic Enzymes

Interactions between drugs, herbs, and nutrients can potentially impact treatment outcomes adversely. Thus, investigating the effects of herbal and nutrient compounds on hepatic metabolic enzymes that govern drug pharmacokinetics is a crucial focus in modern medicine. Singh et al. documented that an 80-percent hydroalcohol extract (at doses of 50 and 100 mg/kg/day for 14 days) of Andrographis paniculata significantly elevated acid-soluble sulfhydryl content, cytochrome P450 (CYP450), cytochrome P450 reductase, cytochrome b5 reductase, glutathione S-transferase, and superoxide dismutase levels at both doses. Moreover, notable increases in catalase, glutathione peroxidase, and glutathione reductase levels were only observed at higher doses[34]. Both aqueous and alcoholic extracts of A. paniculata were found to significantly enhance the activities of CYP1A1 and CYP2B without affecting total hepatic CYP450 contents in male ICR mice[35]. Andrographolide exhibited the significant induction of CYP1A1 and CYP1A2 mRNA expression in cultured mouse hepatocytes, synergizing with CYP1A inducers[36]. A recent report highlighted the noncompetitive inhibition of CYP1A2 and CYP2C, along with competitive inhibition of CYP3A4 in rat and human liver microsomes by A. paniculata extract. In contrast, andrographolide exhibited weak inhibition of rat CYP2E1 exclusively[37]. Comparable effects of the extract and andrographolide on CYP2C and CYP3A

in rat and human hepatocyte cultures were also noted[38]. The current evidence is insufficient to draw definitive conclusions regarding drug-herb interactions. Further comprehensive investigations into hepatic metabolizing enzymes should be conducted in healthy humans as well as those taking medications susceptible to pharmacokinetic changes influenced by these inducible hepatic enzymes.

Antimicrobial and Antiparasitic Effects

Andrographis paniculata has a rich history of use in traditional medicine to address various infectious conditions. Contemporary research has explored its potential against diverse bacteria, viruses, and parasites. Interestingly, powdered crude extract suspended in water displayed no significant in vitro antibacterial activity against Salmonella, Shigella, Escherichia coli, gram A Streptococci, and Staphylococcus aureus, even at a concentration of 25 mg/mL. Additionally, administration of a single oral dose of up to 6 g of the powder to healthy volunteers or daily doses of 0.12-24 g/kg body weight to rats for six months did not manifest any ex vivo antibacterial effects[39]. However, Singha et al. reported notable antibacterial activity of an aqueous extract, attributing it to the combined action of andrographolides and arabinogalactan proteins[40]. A similar outcome was observed by Zaidan et al., who found that crude aqueous leaf extract exhibited significant antimicrobial activity against gram-positive Staphylococcus aureus, methicillin-resistant Staphylococcus aureus (MRSA), and gram-negative Pseudomonas aeruginosa, while it had no effect on Escherichia coli or Klebsiella pneumoniae[41]. The ethanol extract, on the other hand, exhibited no significant activity against enterohemorrhagic E. coli strains[42]. Notably, andrographolide, neoandrographolide, and 14-deoxy-11,12-didehydroandrographolide were reported to be viricidal against herpes simplex virus 1 (HSV-1) without significant cytotoxicity at viricidal concentrations[43].

Furthermore, the alcohol extract of the rhizome demonstrated significant in vitro activity against Ascaris lumbricoides[44]. The chloroform extract exhibited complete inhibition of malarial parasite growth within 24 hours of incubation at a concentration of 0.05 mg/mL. Similar inhibition was achieved within 48 hours using the methanol extract at a concentration of 2.5 mg/mL[45]. Methanol extract also demonstrated a significant inhibitory effect against Plasmodium falciparum with an IC50 of 7.2 µg/mL[46]. The four xanthones – 1,8-dihydroxy-3,7-dimethoxyxanthone, 4,8-dihydroxy-2,7-dimethoxyxanthone, 1,2-dihydroxy-6,8-dimethoxyxanthone, and 3,7,8-trimethoxy-1-hydroxy-xanthone – isolated from the plant's roots exhibited in vitro anti-malarial activity against Plasmodium falciparum and in vivo activity in mice infected with Plasmodium berghei[47]. These xanthones also demonstrated antiprotozoal activity against Trypanosoma brucei, Trypanosoma cruzi, and Leishmania infantum[48]. Additionally, water decoction of the leaves exhibited filaricidal activity in vitro and in dogs[49]. However, the clinical relevance of these findings remains inconclusive as many results are derived from in vitro or ex vivo studies, often employing concentrations that might not be feasible in clinical settings.

Cardiovascular Effects

The aqueous extract of Andrographis paniculata demonstrated a dose-dependent reduction in systolic blood pressure in both spontaneously hypertensive rats (SHRs) and normotensive Wistar-Kyoto rats. This was accompanied by a significant decrease in plasma angiotensin-converting enzyme (ACE) activity and lipid peroxidation in the kidneys of extract-treated SHRs. Notably, these changes were not substantially altered in normotensive Wistar-Kyoto rats, suggesting that its hypotensive effect in hypertensive and normotensive rats is mediated through distinct mechanisms[50]. The hypotensive effects of the n-butanol and aqueous fractions of the crude water extract were counteracted or weakened by phentolamine, hexamethonium, pyrilamine, and cimetidine, but not by propranolol, atropine, or captopril[51]. However, the decrease in mean arterial pressure induced by 14-deoxy-11, 12-didehydroandrographolide (DDA), one of the active diterpenoids, in anesthetized Sprague-Dawley rats was mitigated in the presence of propranolol, hexamethonium, and captopril. Additionally, DDA counteracted the positive chronotropic effect of isoproterenol on isolated rat right atria in a non-competitive, dose-dependent manner[52]. Recent research supported hypotensive and negative chronotropic effects of DDA, indicating that the vascular smooth muscle is the primary site of DDA and high-DDA extract hypotensive activity[53].

Numerous investigations explored the impact of A. paniculata water extract and its active components both before and after experimental myocardial infarction (MI) in animals. In dogs, intravenous administration of a water extract one hour after MI restricted infarct size and reduced the extent of core ischemic areas compared to control dogs. Similar outcomes were observed with flavones extracted from the root[54][55]. Myocardial ischemia-reperfusion injury in dogs led to ultrastructural changes in the ischemic region, marked by increased Ca2+ levels and reduced superoxide dismutase, Ca2+-ATPase, and Na+-K+-ATPase activities. Treatment with A. paniculata extract prevented Ca2+ overload in the ischemic area and maintained enzyme activities[56][57]. An intravenous administration of a refined extract (API0134) post-ischemia induction preserved relatively normal cardiac output and rhythm, while preventing an increase in left ventricle end-diastolic pressure in dogs with experimental ischemia-reperfusion myocardial injury[58]. Andrographolide pretreatment of rat cardiomyocytes was reported to protect them against hypoxia/reoxygenation injury in a time-dependent manner, associated with increased cellular reduced glutathione (GSH) levels and antioxidant enzyme activities[59].

Notably, Wang and Zhao examined A. paniculata effects on restenosis following experimental balloon angioplasty. Pretreatment with the extract prevented atherosclerotic iliac artery stenosis in rabbits induced by de-endothelialization and a high-cholesterol diet. Similarly, the extract significantly hindered restenosis after experimental angioplasty in stenosed arteries, as it inhibited cell growth and DNA synthesis in a dose-dependent manner, akin to the mechanism by which drug-coated stents inhibit cell division[60][61].

Furthermore, both the aqueous extract and active compounds, including andrographolide and DDA, inhibited thrombin-induced platelet aggregation in concentration- and time-dependent manners. Extracts with higher DDA concentrations showed less inhibitory activity compared to extracts with lower DDA concentrations, indicating the presence of other compounds in the water extract with antiplatelet aggregation properties[62]. Andrographolide exhibited dose-dependent inhibition of platelet-activating factor (PAF)-induced platelet aggregation without affecting eicosanoid biosynthesis[7]. An A. paniculata extract significantly reduced ex vivo ADP-induced platelet aggregation in 63 patients with cardiac and cerebral vascular diseases three hours post-administration. Notably, those observed for platelet aggregation after one week experienced even more significant effects. Moreover, serotonin release from platelets was markedly reduced in 20 extract-treated volunteers, while plasma serotonin levels remained unchanged[63].

The evidence regarding hypotensive activity of extracts and certain constituents is consistent, but more research is required to establish mechanisms of action, constituents responsible for hypotensive effects, interactions between constituents and blood pressure-lowering medications, and clinical efficacy in hypertensive individuals. Similarly, further exploration in clinical settings is needed to fully understand the cardiovascular and platelet antiaggregation effects observed in various studies.

Antioxidant and Anti-inflammatory Activities

Numerous researchers have documented the antioxidant and anti-inflammatory properties of Andrographis paniculata and its constituents. Das et al. revealed that the water and ethanol extracts of A. paniculata or andrographolide effectively prevented nicotine-induced inhibition of mitochondrial electron chain complexes, thus averting the subsequent rise in nitric oxide (NO) levels in various brain regions of rats. The water extract demonstrated superior antioxidant activity compared to the ethanol extract, despite having higher flavonoid but lower phenol contents[64][65]. In a study by Verma and Vinayak, the aqueous extract significantly boosted the activities of catalase, superoxide dismutase, and glutathione-S-transferase enzymes, while reducing lactate dehydrogenase activity in lymphoma-bearing AKR mice, thereby enhancing liver defense mechanisms[66]. Meanwhile, a methanol extract exhibited the ability to inhibit the formation of reactive oxygen species (ROS) in vitro and completely suppressed carrageenan-induced inflammation[67].

Furthermore, andrographolide pretreatment was found to effectively attenuate the accumulation of ROS induced by phorbol-12-myristate-13-acetate (PMA) and the adhesion of rat neutrophils caused by N-formyl-methionyl-leucyl-phenylalanine (fMLP)[68]. However, the reversal of PMA-induced ROS formation and fMLP-induced adhesion and transmigration of human neutrophils by andrographolide was only partial. This study suggests that the prevention of ROS production involves direct activation of protein kinase C by PMA as well as down-

regulation of surface Mac-1 expression, a crucial integrin for neutrophil adhesion and transmigration[69].

Inflammation is often associated with excessive levels of nitric oxide (NO) and prostaglandin E2 (PGE2), driven by the expression of inducible isoforms of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) from activated macrophages. Lipopolysaccharide (LPS) triggers the secretion of pro-inflammatory cytokines from macrophages and induces iNOS expression, leading to increased NO production. Macrophages incubated with methanol extract, andrographolide, or neoandrographolide display a concentration-dependent inhibition of LPS-stimulated NO production[70-73]. This reduction in iNOS activity associated with andrographolide may arise from decreased iNOS protein expression[71][72]. Andrographolide is also capable of fully restoring the maximal contractile response of the thoracic aorta to phenylephrine after LPS incubation and mitigating the decline in mean arterial blood pressure in anesthetized rats due to LPS[71]. Neoandrographolide, in contrast to andrographolide, is effective ex vivo in suppressing NO production when macrophages are collected after oral administration of the compound and then subjected to LPS stimulation[69]. Andrographolide further inhibits the increase in tumor necrosis factor-alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor induced by LPS[74]. Neoandrographolide also hinders PGE2 synthesis and TNF-α in LPS-stimulated macrophages, and its oral administration to mice significantly suppresses dimethylbenzene-induced ear edema and acetic acid-induced vascular permeability[75]. An refined extract of A. paniculata (API0134) significantly reduces lipid peroxide and endothelin activities while enhancing the activities of NO, cGMP, and superoxide dismutase in experimental atherosclerotic rabbits[76].

Antihyperglycemic and Hypoglycemic Effects

The water extract of A. paniculata has been demonstrated to significantly counteract glucose-induced hyperglycemia in nondiabetic rabbits following oral administration. Remarkably, this effect does not extend to epinephrine-induced hyperglycemia. Surprisingly, chronic administration of the extract for six weeks showed no discernible impact on fasting blood glucose levels[77]. In contrast, the ethanol extract, when orally administered twice daily over a 14-day period to streptozotocin-induced diabetic rats, exhibited a dose-dependent reduction in fasting serum glucose levels while simultaneously elevating body weight. Furthermore, the extract notably decreased levels of thiobarbituric acid-reactive substances in the liver and kidney in comparison to vehicle-treated rats. Simultaneously, it significantly heightened the activity of superoxide dismutase and catalase enzymes, as well as hepatic glutathione concentrations in diabetic rats[78]. Administering an ethanol extract at a dose of 400 mg/kg body weight, twice daily for two weeks to diabetic rats, resulted in a substantial 49.8-percent reduction in fasting serum triglyceride levels – a reduction greater than that achieved by a 27.7-percent decline with 500 mg/kg body weight metformin administered twice daily over 14 days[79]. Moreover, an aqueous extract of A. paniculata (50 mg/kg body weight) administered to streptozotocin-diabetic rats led to a significant 52.9-percent decrease in blood glucose levels.

Notably, freeze-dried material displayed even more pronounced effects, yielding a remarkable 61.8-percent decline at a lower dose of 6.25 mg/kg body weight[80]. Similar outcomes were replicated by Dandu and Inamdar, who observed that the oral administration of an aqueous extract of A. paniculata leaves (400 mg/kg) led to lowered blood glucose levels in streptozotocin-induced animals, along with heightened activity of superoxide dismutase and catalase. The oral decoction also significantly reduced blood glucose levels in alloxan-induced diabetic rats and curbed food and water intake when contrasted with vehicle-treated diabetic controls[81]. Furthermore, the treatment of diabetic rats with the decoction led to a reduction in mean estrous cycles from eight days to five days[82].

As for andrographolide, it seems to exhibit a dose-dependent reduction in plasma glucose concentration both in streptozotocin-induced diabetic rats and normal rats, with a more pronounced effect observed in the latter. Intriguingly, this contrasts with the water extract, which did not manifest a glucose-lowering effect in normoglycemic rats in a separate study[81]. Andrographolide also counteracts the increase in plasma glucose response to intravenous glucose challenge in normal rats and amplifies the uptake of radioactive glucose by isolated soleus muscle from streptozotocin-diabetic rats, following a concentration-dependent pattern. In addition, repetitive intravenous administration of andrographolide to diabetic rats over three days resulted in increased mRNA and protein levels of glucose transporter (GLUT4) in the soleus muscle, implying that andrographolide's hypoglycemic effect might be attributed to enhanced glucose utilization by skeletal muscle[83]. Conversely, in vitro experiments conducted by Wibudi et al. concluded that A. paniculata's hypoglycemic effect arises from insulin release from pancreatic β-cells through ATP-sensitive potassium channels – a mechanism akin to other insulinotropic antidiabetic agents[84]. Parallel in vitro experiments by Subramanian et al. proposed that the ethanol extract of A. paniculata and andrographolide may produce hypoglycemic effects by inhibiting alpha-glucosidase and alpha-amylase enzymes[85]. These findings suggest that the hypoglycemic and antihyperglycemic activities of the extracts and andrographolide might involve distinct mechanisms in normal and diabetic contexts. The water extract, with its minimal impact on fasting blood glucose levels in nondiabetic animals, could potentially serve as a suitable candidate for further investigation. Ultimately, uncovering blood glucose-lowering constituents in both water and ethanol extracts could yield valuable insights.

Effects on Reproductive Systems

Numerous animal studies have highlighted the impact of **A. paniculata** on both male and female reproductive systems. Initial accounts involving oral administration of powdered stem indicated an antifertility effect in male Wistar mice, while fertility remained unaffected in female mice[86,87]. Similarly, reports exist of **A. paniculata** administration leading to abortion in pregnant rabbits[6].

Intraperitoneal injection of an aerial parts decoction in female albino mice was shown to prevent implantation and induce abortion during various gestation periods. Notably, early pregnancy

termination occurred following intramuscular, subcutaneous, and intravenous administration. The administration of progesterone or luteinizing hormone-releasing hormone effectively counteracted or significantly mitigated the abortifacient effects. This observation suggests a potential mechanism involving interference with progesterone activity contributing to the abortifacient effect. Furthermore, the herb was found to curtail the growth of human placental chorionic trophoblastic cells in vitro[6].

Zoha et al. conducted an experiment involving female mice fed sun-dried **Andrographis** powder at a dose of 2 g/kg body weight/day for six weeks. Intriguingly, upon mating with untreated fertile males, 100 percent of the treated female mice exhibited pregnancy inhibition. Conversely, over 95 percent of untreated female mice in the control group became pregnant under similar circumstances[88].

Meanwhile, Akbarsha et al. administered dry leaf powder to male albino rats (20 mg daily for 60 days), leading to inhibited spermatogenesis, degenerative changes in seminiferous tubules, regression of Leydig cells, and regressive and/or degenerative alterations in the epididymis, seminal vesicle, ventral prostate, and coagulating glands[89]. Akin results were observed when andrographolide was orally administered to male Wistar albino rats for 48 days. This administration resulted in reduced sperm count, diminished sperm motility, and noted sperm abnormalities[90]. However, Burgos et al. contradicted these findings, reporting no testicular toxicity in male Sprague Dawley rats even when exposed to standardized dried extract at doses up to 1,000 mg/kg daily for 60 days. Their assessment was based on testicular weight and histology, ultrastructural examination of Leydig cells, and testosterone levels[91]. Moreover, **A. paniculata** extract, when administered orally at doses of 200, 600, and 2,000 mg/kg daily during the initial 19 days of pregnancy, did not impact progesterone levels in pregnant rats[92]. Notably, Burgos et al. revealed that the dried extract of **A. paniculata** induces uterine relaxation by inhibiting voltage-sensitive calcium channels[93]. In a phase I clinical study involving Kan-Jang (a combination of **A. paniculata** and *Eleutherococcus senticosus*), no significant negative effects on sperm quality and fertility in healthy adult males were reported[94].

The current body of evidence is marked by inconsistencies, with certain findings directly contradicting others. As such, drawing definitive conclusions about the reproductive effects of **A. paniculata** proves challenging. However, existing evidence does seem to suggest that **A. paniculata** is unlikely to function as an effective form of birth control. Consequently, further exploration of short- and long-term effects on fertility remains imperative.

Conclusions and Other Potential Uses

The consistent hepatoprotective effects observed with various extracts and constituents of A. paniculata highlight its potential efficacy. Its inclusion in effective polyherbal formulations for liver ailments that lack modern interventions underscores its promise. Nonetheless, conclusive findings demand further investigation, particularly regarding its impact on post-hepatic damage. Understanding how A. paniculata or its constituents reverse pathological

changes and identifying the most effective form is essential. Further research is also imperative to assess its influence on liver-metabolizing enzymes and potential drug interactions.

The variability in in vitro antibacterial effects could stem from various factors, with variations in tested material constituents being a significant factor. Discrepancies have been reported from different regions, such as positive results from India and Malaysia, and negative results from Thailand. Elements like plant collection, storage conditions, and extraction methods may affect constituent profiles. Consequently, establishing a clear link between antimicrobial activity and constituent presence is crucial when evaluating crude preparations.

A. paniculata has demonstrated notable effects on blood pressure and cardiovascular conditions in experimental studies. However, its clinical use in hypertensive situations requires deeper research to comprehensively understand the plant's impact on blood pressure regulation. Similar in-depth exploration is warranted for other cardiovascular conditions where potential effectiveness has been suggested, such as infarct size reduction, cardiac function maintenance under ischemic conditions, platelet aggregation prevention, and restenosis inhibition after angioplasty.

Remarkable antihyperglycemic activity has been observed in diabetic rats with both water and alcohol extracts of A. paniculata. The alcohol extract, in particular, exhibited significant reduction in serum triglyceride levels, outperforming metformin treatment. Proposed mechanisms include increased antioxidant enzyme activity, better glucose utilization via upregulation of GLUT4, and enhanced insulin release. However, these mechanisms necessitate further exploration.

The existing evidence strongly supports A. paniculata's potential role in treating upper respiratory tract infections (URTI), and it might also accelerate the course of other self-limited infections.

Declarations

Ethics approval and consent to participate

The conducted research does not pertain to the involvement of either human or animal subjects.

Consent for publication

I, the undersigned, give my consent for the publication of identifiable details, which can include photograph(s) and/or videos and/or case history and/or details within the text (“Material”) to be published in the above Journal and Article.

Availability of data and materials

not applicable

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