Asian Journal of Research in Biochemistry

Volume 13, Issue 2, Page 28-37, 2023; Article no.AJRB.106050
ISSN: 2582-0516

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

Nandini Premkumar [a++*]

[a] *Department of Botany, Bangalore University, Bangalore-560056, India.*

Author's contribution

Author NP conceived and designed the study, conducted the research, collected and analyzed the data, interpreted the results, wrote and approved the manuscript.

Article Information

DOI: 10.9734/AJRB/2023/v13i2253

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/106050

Review Article

Received: 30/06/2023
Accepted: 02/09/2023
Published: 06/09/2023

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.

[++]*Student;*
**Corresponding author: E-mail: klrnandini@gmail.com;*

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

1. INTRODUCTION

Andrographis paniculata, a valued component of traditional Asian medicine, is renowned for its role in treating various conditions [1,2]. It is particularly noted for its ability to purify blood, making it indispensable for managing conditions like skin eruptions, boils, scabies, and persistent fevers [1]. This plant's medicinal use mainly involves its aerial parts, which contain a diverse range of chemical compounds such as lactones, diterpenoids, flavonoids, and glycosides [1]. Clinical trials support its effectiveness in alleviating symptoms of uncomplicated upper respiratory tract infections [1].

While A. *paniculata* has been a staple in traditional healing systems [2], its benefits deserve careful evaluation due to the self-limiting nature of many conditions it addresses. This review highlights current scientific findings and emphasizes the need for comprehensive research to validate its therapeutic efficacy [3,4].

Known as "Chirayetah" and "Kalmegh" in Urdu and Hindi, this annual plant grows to 1 to 3 feet and is revered in Unani and Ayurvedic traditions [2]. Also known as "Creat" and "king of bitters," it thrives in India and across Asia, where it holds a significant place in traditional medicine [2].

Though primarily using the plant's aerial parts, historical records suggest the utilization of the whole plant or its roots for specific therapeutic purposes [2]. Traditional forms of consumption included infusion, decoction, or powder, either alone or in combination with other herbs [2]. Today, commercial preparations often focus on standardized whole-plant extracts, bridging tradition and modernity [2].

Given the self-limiting nature of many conditions traditionally treated with A. *paniculata*, it's essential to critically consider its claimed benefits [3,4]. This synthesis presents existing scientific knowledge and points toward areas deserving further exploration. The references provided serve as a foundation for understanding the healing potential of Andrographis paniculata.

2. TRADITIONAL APPLICATIONS OF *Andrographis paniculata* IN MEDICINE

A. *paniculata* exhibits diverse benefits, including antibacterial, antifungal, and antiviral properties [3]. In Unani medicine, it serves as an aperient, anti-inflammatory, liver tonic, and more [1]. It addresses conditions like skin issues, fevers, irregular bowel habits, and debility [2,4,5].

In Chinese medicine, A. *paniculata* treats *pharyngolaryngitis*, diarrhea, snakebites, and more [6]. It dispels pathogenic heat and proves effective against infectious and non-infectious diseases [6].

3. 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].

4. PHYTOCONSTITUENTS COMPOSITION

In A. *paniculata*, various phytoconstituents exist, including diterpenes, lactones, and flavonoids. Flavonoids are mainly in the roots but also in the leaves. Aerial parts contain alkanes, ketones, and aldehydes. Bitterness was attributed to andrographolide, but *kalmaghin* is another bitter component. China identified four lactones (Chuan Xin Lian A, B, C, D) from aerial parts. Leaves hold a diterpene glucoside (deoxyandrographolide 19beta-D-glucoside), six ent-labdane diterpenoids, and more [14-16]. The whole plant yielded identified flavonoids. Recent findings include 12 new flavonoids, 14 diterpenoids, two flavonoid glycosides, a new diterpenoid (andrographic acid), and two ent-labdane diterpenoid glycosides from aerial parts [6,17-20].

5. MECHANISMS OF OPERATION HEPATOPROTECTIVE EFFECTS

A. *paniculata* is widely used in Indian traditional medicine for its hepato-stimulant and hepatoprotective properties [21]. It's part of polyherbal formulations for hepatoprotection [22], even showing effectiveness against chronic hepatitis B [23]. Andrographolide, the main active compound, has significant choleretic effects,

surpassing silymarin in protecting against acetaminophen-induced bile reduction [24]. Combining arabinogalactan proteins and andrographolide provided hepatoprotection against ethanol-induced damage comparable to silymarin [25]. A. *paniculata* extract protected rats from ethanol-induced serum transaminase elevation [26], and it showed protection against hepatic lipid peroxidation induced by CCl4 [27]. Crude alcohol extracts from leaves also exhibited hepatoprotective effects against CCl4-induced liver damage [28].

Studies showed that andrographolide, the methanol extract of the whole plant, and andrographolide-free methanol extract inhibited CCl4-induced liver damage in rats, indicating A. *paniculata's* constituents beyond andrographolide play a hepatoprotective role [29]. Andrographolide exhibited protective effects against hepatotoxicity induced by various agents, comparable to or exceeding the effects of compounds like *andrographolide* and *neoandrographolide* [30]. Both A. Protection against oxidative stress and liver damage in mice was provided by *paniculata* extract and *andrographolide*, as indicated by studies [31-33].

The experiments used different extracts and components, all displaying hepatoprotective effects. A. *paniculata's* constituents seem to possess broad-spectrum hepatoprotective effects, warranting further research to determine the most effective component(s) and their efficacy in treating diverse liver diseases [21-33].

6. INFLUENCE ON HEPATIC METABOLIC ENZYMES

Investigating interactions between drugs, herbs, and nutrients that affect hepatic metabolic enzymes is crucial for treatment outcomes. An 80% hydroalcohol extract of Andrographis paniculata increased acid-soluble sulfhydryl content and levels of enzymes like cytochrome P450 (CYP450), cytochrome P450 reductase, and superoxide dismutase in rats [34]. Aqueous and alcoholic extracts boosted CYP1A1 and CYP2B activities without affecting total hepatic CYP450 content in male mice [35]. Andrographolide-induced CYP1A1 and CYP1A2 mRNA expression in mouse hepatocytes synergistically with CYP1A inducers [36]. A study noted noncompetitive inhibition of CYP1A2 and CYP2C, and competitive inhibition of CYP3A4 by A. *paniculata* extract in rat and human liver microsomes, while andrographolide weakly inhibited rat CYP2E1 [37]. Similar effects were seen in rat and human hepatocyte cultures for CYP2C and CYP3A inhibition by both the extract and andrographolide [38]. Definitive conclusions about drug-herb interactions are lacking. Further research on hepatic metabolizing enzymes in healthy humans and those taking medications susceptible to pharmacokinetic changes by these enzymes is needed.

7. ANTIMICROBIAL AND ANTIPARASITIC EFFECTS

Andrographis paniculata has historical use in traditional medicine for infectious conditions. Research has explored its potential against bacteria, viruses, and parasites. Powdered crude extract in water showed no significant antibacterial effects *in vitro* against various bacteria, even at high concentrations. Oral doses up to 6 g in humans and 0.12-24 g/kg in rats had no ex vivo antibacterial effects [39]. However, an aqueous extract showed notable antibacterial activity attributed to andrographolides and arabinogalactan proteins [40]. Similar outcomes were seen with crude aqueous leaf extract against gram-positive bacteria but not *E. coli* or *K. pneumonia* [41,42]. *Andrographolide*, *neoandrographolide*, and 14-deoxy-11,12-*didehydroandrographolide* exhibited viricidal effects against herpes simplex virus 1 (HSV-1) without cytotoxicity at effective concentrations [43].

The alcohol extract of the rhizome displayed significant *in vitro* activity against Ascaris lumbricoides [44]. The chloroform extract completely inhibited malarial parasite growth within 24 hours at 0.05 mg/mL, and methanol extract showed similar inhibition within 48 hours at 2.5 mg/mL [45]. Methanol extract also significantly inhibited Plasmodium falciparum with an IC50 of 7.2 µg/mL [46]. Xanthones from the plant's roots exhibited *in vivo* and *in vitro* anti-malarial activity against *Plasmodium* berghei and Plasmodium falciparum [47]. These xanthones also showed antiprotozoal activity against *Trypanosoma brucei*, *Trypanosoma cruzi,* and *Leishmania infantum* [48]. Water decoction of the leaves exhibited filaricidal activity *in vitro* and in dogs [49]. However, clinical relevance is uncertain due to *in vitro*/ex vivo studies with potentially non-feasible concentrations.

8. CARDIOVASCULAR EFFECTS

The aqueous extract of Andrographis paniculata reduced systolic blood pressure in hypertensive

and normotensive rats, linked to ACE activity reduction and kidney lipid peroxidation in hypertensive rats [50]. The hypotensive effects of n-butanol and aqueous fractions were influenced by certain agents [51]. 14-deoxy-11,12-didehydroandrographolide (DDA) reduced blood pressure and heart rate in rats, affected by propranolol, hexamethonium, and captopril [52]. DDA demonstrated hypotensive and negative chronotropic effects through vascular smooth muscle action [53].

A. *paniculata's* effects on experimental myocardial infarction were explored. In dogs, the extract restricted infarct size and ultrastructural changes [54,55]. Post-ischemia extract administration maintained cardiac output and rhythm, preventing ventricle end-diastolic pressure increase [56-58]. Andrographolide protected rat cardiomyocytes from hypoxia/reoxygenation injury, raising glutathione levels and antioxidant enzyme activities [59].

In rabbits, the extract prevented atherosclerotic stenosis and hindered restenosis post-angioplasty [60,61]. Aqueous extract, andrographolide, and DDA inhibited platelet aggregation in various ways [62]. A. *paniculata* extract reduced platelet aggregation and serotonin release in patients [63].

While evidence supports hypotensive and cardiovascular effects, more research is needed on mechanisms, constituents' roles, interactions, and clinical efficacy. Further investigation is required to comprehend cardiovascular and platelet effects in clinical scenarios.

9. ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITIES

Researchers have highlighted Andrographis paniculata's antioxidant and anti-inflammatory properties. Water and ethanol extracts, along with andrographolide, prevented nicotine-induced mitochondrial electron chain complex inhibition, curbing nitric oxide (NO) increase in rat brain regions [64,65]. Aqueous extract enhanced liver defense enzymes and reduced lactate dehydrogenase activity in lymphoma-bearing mice [66]. Methanol extract inhibited reactive oxygen species (ROS) formation and suppressed carrageenan-induced inflammation [67]. Andrographolide reduced ROS accumulation induced by phorbol-12-myristate-13-acetate (PMA) and neutrophil adhesion caused by N-formyl-methionyl-leucyl-phenylalanine (fMLP) [68,69].

Inflammation involves excessive NO and prostaglandin E2 (PGE2) levels from iNOS and COX-2 expression in activated macrophages. Methanol extract, andrographolide, and neoandrographolide inhibited LPS-stimulated NO production, possibly via reduced iNOS expression [70-73]. Andrographolide restored aorta response after LPS incubation and mitigated blood pressure decline in rats due to LPS [71]. Neoandrographolide suppressed NO production ex vivo after oral administration [69].

Andrographolide inhibited TNF-α and granulocyte-macrophage colony-stimulating factor induced by LPS [74]. Neoandrographolide hindered PGE2 synthesis, TNF-α, and reduced edema and vascular permeability in mice [75]. A refined A. *paniculata* extract reduced lipid peroxide, and endothelin, and enhanced NO, cGMP, and superoxide dismutase activities in atherosclerotic rabbits [76].

10. ANTIHYPERGLYCEMIC AND HYPOGLYCEMIC EFFECTS

A. *paniculata* extracts and andrographolide exhibit antihyperglycemic effects. The water extract effectively counters glucose-induced hyperglycemia in nondiabetic rabbits, with no impact on epinephrine-induced hyperglycemia or fasting blood glucose levels [77]. Ethanol extract reduces fasting serum glucose in diabetic rats, elevating body weight, and enhancing antioxidant enzyme activities [78]. An ethanol extract significantly reduces fasting serum triglycerides in diabetic rats more than metformin [79]. Aqueous extract decreases blood glucose levels in streptozotocin-diabetic rats, with freeze-dried material showing pronounced effects [80]. Oral administration of A. *paniculata* leaves reduces blood glucose levels, increases antioxidant activity, and curbs food and water intake in diabetic animals [81]. Andrographolide reduces plasma glucose concentration dose-dependently in diabetic and normal rats, possibly by enhancing glucose utilization and insulin release [82,83,84]. Both extracts and andrographolide may inhibit alpha-glucosidase and alpha-amylase enzymes, contributing to hypoglycemic effects [85]. The extracts and andrographolide may employ distinct mechanisms for hypoglycemic effects in different contexts. The water extract's limited effect on fasting blood glucose in nondiabetic animals could warrant further exploration to uncover potential blood glucose-lowering constituents [77,81].

11. EFFECTS ON REPRODUCTIVE SYSTEMS

A. *paniculata's* effects on reproductive systems are conflicting. In male Wistar mice, powdered stem administration displayed antifertility effects, while fertility remained unaffected in females [86,87]. Administration of aerial parts decoction induced abortion and prevented implantation in female albino mice, possibly involving interference with progesterone activity [6]. Female mice fed sun-dried Andrographis powder exhibited pregnancy inhibition [88]. In male albino rats, A. *paniculata* leaf powder inhibited spermatogenesis, while andrographolide administration to male rats reduced sperm count and motility [89,90]. However, other studies reported no testicular toxicity in rats exposed to A. *paniculata* extract [91]. A. *paniculata* extract did not affect progesterone levels in pregnant rats and induced uterine relaxation by inhibiting calcium channels [92,93]. A clinical study showed no significant impact on sperm quality and fertility in healthy adult males [94]. Inconsistencies exist, making it challenging to draw definitive conclusions, but A. *paniculata's* effectiveness as birth control seems unlikely. Further research into short- and long-term fertility effects is necessary [95-101].

12. CONCLUSIONS AND OTHER POTENTIAL USES

A. *paniculata's* consistent hepatoprotective effects and its inclusion in polyherbal formulations for liver ailments emphasize its potential, though further investigation is needed. Variability in antibacterial effects might arise from diverse factors, including constituent variations due to collection and extraction methods. A. *paniculata's* impact on blood pressure, cardiovascular conditions, and platelet aggregation is promising but requires comprehensive clinical research. Antihyperglycemic activity is evident in diabetic rats, driven by mechanisms like enhanced antioxidant activity, improved glucose utilization, and insulin release, which merit further study. The evidence supports A. *paniculata's* potential for treating URTIs and self-limited infections.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my Mentor Dr.Maya C N, Bangalore University, for their invaluable guidance and support throughout the research process. Their insights and feedback greatly contributed to the development of this work.

I am also thankful to Bangalore University for engaging discussions and feedback that helped refine the ideas presented in this article.

Lastly, I am grateful to my family and friends for their unwavering encouragement and understanding during the writing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Kabeeruddin M, Kitabul Advia. Aligarh Barqi Press, Delhi, India. 1937;2:148.
2. Dymock W. Pharmacographia Indica. The Institute of Health and Tibbi Research, Hamdard National Foundation, Pakistan. 1972; 44.
3. Bhatnagar SS, Desa JD, et al, Santapau H. Biological activity of Indian medicinal plants. Indian J Med Res 1961;49:799-813.
4. Chopra RN, Chopra IC, Kapur LD, Handa KL,. Indigenous Drugs of India. India: Academic Publishers; 1982:238.
5. Khory RN, Katrak NN. Materia Medica of India and Their Therapeutics. India: Neeraj Publishing House; 1984:64.
6. Chang HM, But PPH. Pharmacology and Applications of Chinese Materia Medica. English translation by Shem Chang-Shing Yeung, Sih Cheng-Yao and Lai-Ling Wang (Chinese Medicinal Material Research Centre, The Chinese University of Hong Kong), Singapore: World Scientific Publishing Co. Pte. Ltd. 1987;2:918-928.
7. Amroyan E, Panossian A, Gabrielian E, et al. Inhibitory effect of andrographolide from *Andrographis* paniculata on PAF-induced platelet aggregation. Phytomedicine. 1999;6:27-31.
8. See D, Roshan R, Mason S. Increased tumor necrosis factor alpha (TNF-alpha) and natural killer cell (NK) function using an integrative approach in late stage cancers. Immunol Invest. 2002;31:137-153.
9. Sheeja K, Kuttan G, Guruvayoorappan C. Antiangiogenic activity of *Andrographis paniculata* extract and andrographolide. Int Immunopharmacol. 2007;7:211-221.

10. Shi MD, Lee YC, Lin HH, et al. Inhibition of cell-cycle progression in human colorectal carcinoma Lovo cells by andrographolide. Chem Biol Interact. 2008;174:201-210.
11. Yang L, Luo K, Wu D, et al. Andrographolide enhances 5-fluorouracil-induced apoptosis via caspase-8-dependent mitochondrial pathway involving p53 participation in hepatocellular carcinoma (SMMC-7721) cells. Cancer Lett. 2009;276:180-188.
12. Zhao F, Wang L, He EQ, Liu K. Anti-tumor activities of andrographolide, a diterpene from *Andrographis paniculata*, by inducing apoptosis and inhibiting VEGF level. J Asian Nat Prod Res. 2008;10:467-473.
13. Calabrese C, Babish JG, Berman SH, et al. A phase I trial of andrographolide in HIV positive patients and normal volunteers. Phytother Res. 2000;14:333-338.
14. Weiming C, Xiaotian L. Deoxyandrographolide19beta-D-glucoside from the leaves of *Andrographis paniculata*. Planta Med. 1982;45:245-246.
15. Matsuda T, Sugiyama S, Kuroyanagi M, et al. Cell differentiation-inducing diterpenes from *Andrographis paniculata* Nees. Chem Pharm Bull (Tokyo). 1994;42:1216-1225.
16. Koteswara Rao Y, Rao CV, Vimalamma G, Tzeng YM. Flavonoids and andrographolides from *Andrographis paniculata*. Phytochemistry. 2004;65:2317-2321.
17. Chen LX, Qiu F, Qu GX. Studies on flavonoids of *Andrographis paniculata*. Zhongguo Zhong Yao Za Zhi. 2006;31:391-395. [Article in Chinese]
18. Chen LX, Qiu F, Qu GX. Studies on diterpenoids from *Andrographis paniculata*. Zhongguo Zhong Yao Za Zhi. 2006;31:1594-1597. [Article in Chinese]
19. Li W, Zhang H, Xu X, et al. Secondary metabolites from *Andrographis paniculata*. Chem Pharm Bull (Tokyo). 2007;55:455-458.
20. Zhou KL, Zhuang YL, Chen LX. et al. Two new ent-labdane diterpenoid glycosides from the aerial parts of *Andrographis paniculata*. J Asian Nat Prod Res. 2008; 10:939-943.
21. Trivedi NP, Rawal UM. Hepatoprotective and antioxidant property of *Andrographis paniculata* (Nees) in BHC-induced liver damage in mice. India. Indian J Exp Biol. 2001;39:41-46.
22. Ram VJ. Herbal preparations as a source of hepatoprotective agents. India, Drug News Perspect. 2001;14:353-363.
23. Rajkumar JS, Sekar MG, Mitra SK. Safety and efficacy of oral HD-03/ES given for six months in patients with chronic hepatitis B virus infection. India, World J Gastroenterol. 2007;13:4103-4107.
24. Shukla B, Visen PK, Patnaik GK, Dhawan BN. Choleretic effect of andrographolide in rats and guinea pigs. India, Planta Med. 1992;58:146-149.
25. Singha PK, Roy S, Dey S. Protective activity of andrographolide and arabinogalactan proteins from *Andrographis paniculata* Nees against ethanol-induced toxicity in mice. J Ethnopharmacol. 2007;111:13-21.
26. Choudhury BR, Poddar MK. Effect of Kalmegh extract on rat liver and serum enzymes. Methods Find Exp Clin Pharmacol. 1983;5:727-730.
27. Choudhury BR, Poddar MK. Andrographolide and kalmegh (*Andrographis paniculata*) extract: *In vivo* and *in vitro* effect on hepatic lipid peroxidation. Methods Find Exp Clin Pharmacol. 1984;6:481-485.
28. Rana AC, Avadhoot Y. Hepatoprotective effects of *Andrographis paniculata* against carbon tetrachloride-induced liver damage. Arch Pharm Res. 1991;14:93-95.
29. Handa SS, Sharma A. Hepatoprotective activity of andrographolide against carbon tetrachloride. Indian J Med Res 1990;92:276-283.
30. Kapil A, Koul IB, Banerjee SK, Gupta BD. Antihepatotoxic effects of major diterpenoid constituents of *Andrographis paniculata*. Biochem Pharmacol. 1993;46:182-185.
31. Trivedi NP, Rawal UM, Patel BP. Hepatoprotective effect of andrographolide against hexachlorocyclohexane-induced oxidative injury. Integr Cancer Ther. 2007; 6:271-280.
32. Handa SS, Sharma A. Hepatoprotective activity of andrographolide against galactosamine and paracetamol intoxication in rats. Indian J Med Res. 1990;92:284-292.
33. Visen PK, Shukla B, Patnaik GK, Dhawan BN. Andrographolide protects rat hepatocytes against paracetamol-induced damage. J Ethnopharmacol. 1993;40:131-136.
34. Singh RP, Banerjee S, Rao AR. Modulatory influence of *Andrographis paniculata* on

mouse hepatic and extrahepatic carcinogen metabolizing enzymes and antioxidant status. Phytother Res. 2001; 15:382-390.

35. Jarukamjorn K, Don-in K, Makejaruskul C, et al. Impact of *Andrographis paniculata* crude extract on mouse hepatic cytochrome P450 enzymes. J Ethnopharmacol. 2006;105:464-467.
36. Jaruchotikamol A, Jarukamjorn K, Sirisangtrakul W, et al. Strong synergistic induction of CYP1A1 expression by andrographolide plus typical CYP1A inducers in mouse hepatocytes. Toxicol Appl Pharmacol. 2007;224:156-162.
37. Pekthong D, Martin H, Abadie C, et al. Differential inhibition of rat and human cytochrome P450 by *Andrographis paniculata* extract and andrographolide. J Ethnopharmacol. 2008;115:432-440.
38. Pekthong D, Blanchard N, Abadie C, et al. Effects of *Andrographis paniculata* extract and Andrographolide on hepatic cytochrome P450 mRNA expression and monooxygenase activities after *in vivo* administration to rats and *in vitro* in rat and human hepatocyte cultures. Chem Biol Interact. 2009;79:247-255.
39. Leelarasamee A, Trakulsomboon S, Sittisomwong N. Undetectable anti-bacterial activity of *Andrographis paniculata* (Burma) wall. ex ness. J Med Assoc Thai. 1990;73:299-304.
40. Singha PK, Roy S, Dey S. Antimicrobial activity of *Andrographis paniculata*. Fitoterapia. 2003;74:692-694.
41. Zaidan MR, Noor Rain A, Badrul AR, et al. *In vitro* screening of five local medicinal plants for antibacterial activity using disc diffusion method. Trop Biomed. 2005;22: 165-170.
42. Voravuthikunchai SP, Limsuwan S. Medicinal plant extracts as anti-Escherichia coli O157:H7 agents and their effects on bacterial cell aggregation. J Food Prot. 2006;69:2336-2341.
43. Wiart C, Kumar K, Yusof MY, et al. Antiviral properties of ent-labdene diterpenes of *Andrographis paniculata* Nees, inhibitors of herpes simplex virus type 1. Phytother Res. 2005;19:1069-1070.
44. Kaleysa Raj R. Screening of indigenous plants for anthelmintic action against human Ascaris lumbricoides. Part I. Indian J Physiol Pharmaco.l 1975;19:47-49.
45. Najib Nik A, Rahman N, Furuta T, et al. Antimalarial activity of extracts of Malaysian medicinal plants. J Ethnopharmacol. 1999;64:249-254.
46. Mishra K, Dash AP, Swain BK, Dey N. Anti-malarial activities of *Andrographis paniculata* and Hedyotis corymbosa extracts and their combination with curcumin. Malar. J 2009;8:26.
47. Dua VK, Ojha VP, Roy R, et al. Antimalarial activity of certain xanthones isolated from the roots of *Andrographis paniculata*. J Ethnopharmacol. 2004;95:247-251.
48. Dua VK, Verma G, Dash AP. *In vitro* antiprotozoal activity of selected xanthones from the roots of *Andrographis paniculata*. Phytother Res. 2009;23:126-128.
49. Dutta A, Sukul NC. Filaricidal properties of the wild herb *Andrographis paniculata*. J Helminthol. 1982;56:81-84.
50. Zhang CY, Tan BK. Hypotensive activity of aqueous extract of *Andrographis paniculata* in rats. Clin Exp Pharmacol Physiol. 1996; 23:675-678.
51. Zhang CY, Tan BK. Mechanism of cardiovascular effects of *Andrographis paniculata* in anesthetized rats. J Ethnopharmacol. 1997;56:97-101.
52. Zhang CY, Kuroyangi, Tan BK. Cardiovascular activity of 14-deoxy-11,12-didehydro-andrographolide in anesthetized rats and isolated right atria. Pharmacol Res. 1998;38:413-417.
53. Yoopan N, Visada Prachayasittikul, Rangkadilok N, et al. Cardiovascular effects of 14-deoxy-11,12-didehydroandrographolide and *Andrographis paniculata* extracts. Planta Med. 2007;73:503-511.
54. Zhao HY, Fang WY. Protective effects of *Andrographis paniculata* Nees on post-infarction myocardium in experimental dogs. J Tongji Med Univ. 1990;10:212-217.
55. Zhao HY, Fang WY. Antithrombotic effects of *Andrographis paniculata* Nees in preventing myocardial infarction. Chinese Med J (Engl). 1991;104:770-775.
56. Guo ZL, Zhao HY, Zheng XH. Effect of *Andrographis paniculata* Nees in alleviating myocardial ischemic reperfusion injury. J Tongji Med Univ. 1994;14:49-51.
57. Guo ZL, Zhao HY, Zheng XH. Mechanism of *Andrographis paniculata* Nees in alleviating Ca2+-overloading during myocardial ischemic reperfusion. J Tongji Med Univ. 1995;15:205-208.
58. Guo ZL, Zhao H, Fu L. Protective effects of API0134 on myocardial ischemia and

reperfusion injury. J Tongji Med Univ. 1996; 16:193-197.
59. Woo AY, Waye MM, Tsui SK, et al. Andrographolide up-regulates cellular reduced glutathione level and protects cardiomyocytes against hypoxia/ reoxygenation injury. J Pharmacol Exp Ther 2008;325:226-235.
60. Wang DW, Zhao HY. Experimental studies on the prevention of atherosclerotic arterial stenosis and restenosis after angioplasty with *Andrographis paniculata* Nees and fish oil. J Tongji Med Univ. 1993;13:193-198.
61. Wang DW, Zhao HY. Prevention of atherosclerotic arterial stenosis and restenosis after angioplasty with *Andrographis paniculata* Nees and fish oil. Experimental studies on effects and mechanisms. Chinese Med J (Engl). 1994; 107:464-470.
62. Visada Prachayasittikul, Rangkadilok N, Pholphana N. et al. Inhibitory effect of *Andrographis paniculata* extract and its active diterpenoids on platelet aggregation. Eur J Pharmacol. 2006;553:39-45.
63. Zhang YZ, Tang JZ, Zhang YJ. Study of *Andrographis paniculata* extracts on antiplatelet aggregation and release reaction and its mechanism. Zhongguo Zhong Xi Yi Jie He Za Zhi. 1994;14:28-35. [Article in Chinese]
64. Das S, Gautam N, Dey SK, et al. Oxidative stress in the brain of nicotine-induced toxicity: Protective role of *Andrographis paniculata* Nees and vitamin E. Appl Physiol Nutr Metab. 2009;34:124-135.
65. Lin FL, Wu SJ, Lee SC, Ng LT. Antioxidant, antioedema, and analgesic activities of *Andrographis paniculata* extracts and their active constituent andrographolide. Phytother Res 2009;23:958-964.
66. Verma N, Vinayak M. Antioxidant action of *Andrographis paniculata* on lymphoma. Mol Biol Rep. 2008;35:535-540.
67. Sheeja K, Shihab PK, Kuttan G. Antioxidant and anti-inflammatory activities of the plant *Andrographis paniculata* Nees. Immunopharmacol Immunotoxicol. 2006; 28:129-140.
68. Shen YC, Chen CF, Chiou WF. Suppression of rat neutrophil reactive oxygen species production and adhesion by the diterpenoid lactone andrographolide. Planta Med. 2000;66: 314-317.
69. Shen YC, Chen CF, Chiou WF. Andrographolide prevents oxygen radical production by human neutrophils: Possible mechanism(s) involved in its anti-inflammatory effect. Br J Pharmacol. 2002; 135:399-406.
70. Batkhuu J, Hattori K, Takano F, et al. Suppression of NO production in activated macrophages *in vitro* and ex vivo by neoandrographolide isolated from *Andrographis paniculata*. Biol Pharm Bull. 2002;25:1169-1174.
71. Chiou WF, Lin JJ, Chen CF. Andrographolide suppresses the expression of inducible nitric oxide synthase in macrophages and restores vasoconstriction in rat aorta treated with lipopolysaccharide. Br J Pharmacol. 1998;125:327-334.
72. Chiou WF, Chen CF, Lin JJ. Mechanism of suppression of inducible nitric oxide synthase (iNOS) expression in RAW 264.7 cells by andrographolide. Br J Pharmacol. 2000;129:1553-1560.
73. Liu J, Wang ZT, Ji LL, Ge BX. Inhibitory effects of neoandrographolide on nitric oxide and prostaglandin E2 production in LPS-stimulated murine macrophage. Mol Cell Biochem. 2007;298:49-57.
74. Abu-Ghefreh AA, Canatan H, Ezeamuzie CI. *In vitro* and *in vivo* anti-inflammatory effects of andrographolide. Int Immunopharmacol. 2009;9:313-318.
75. Liu J, Wang ZT, Ji LL. *In vivo* and *in vitro* anti-inflammatory activities of neoandrographolide. Am J Chin Med. 2007;35:317-328.
76. Wang HW, Zhao HY, Xiang SQ. Effects of *Andrographis paniculata* component on nitric oxide, endothelin, and lipid peroxidation in experimental atherosclerotic rabbits. Zhongguo Zhong Xi Yi Jie He Za Zhi. 1997;17:547-549. [Article in Chinese]
77. Borhanuddin M, Shamsuzzoha M, Hussain AH. Hypoglycemic effects of *Andrographis paniculata* Nees on non-diabetic rabbits. Bangladesh Med Res Counc Bull. 1994; 20:24-26.
78. Zhang XF, Tan BK. Antihyperglycemic and antioxidant properties of *Andrographis paniculata* in normal and diabetic rats. Clin Exp Pharmacol Physiol. 2000;27:358-363.
79. Zhang XF, Tan BK. Antidiabetic property of ethanolic extract of *Andrographis paniculata* in streptozotocin-diabetic rats.

Acta Pharmacol Sinica. 2000;21:1157-1164.
80. Husen R, Pihie AH, Nallappan M. Screening for antihyperglycemic activity in several local herbs of Malaysia. J Ethnopharmacol. 2004;95:205-208.
81. Dandu AM, Inamdar NM. Evaluation of beneficial effects of antioxidant properties of aqueous leaf extract of *Andrographis paniculata* in STZ-induced diabetes. Pak J Pharm Sci. 2009;22:49-52.
82. Reyes BA, Bautista ND, Tanquilut NC, et al. Anti-diabetic potentials of Momordica charantia and *Andrographis paniculata* and their effects on estrous cyclicity of alloxan-induced diabetic rats. J Ethnopharmacol. 2006;105:196-200.
83. Yu BC, Hung CR, Chen WC, Cheng JT. Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats. Planta Med. 2003;69:1075-1079.
84. Wibudi A, Kiranadi B, Manalu W, et al. The traditional plant, *Andrographis paniculata* (Sambiloto), exhibits insulin-releasing actions *in vitro*. Acta Med Indones. 2008; 40:63-68.
85. Subramanian R, Asmawi MZ, Sadikun A. *In vitro* alpha-glucosidase and alpha-amylase enzyme inhibitory effects of *Andrographis paniculata* extract and andrographolide. Acta Biochim Pol. 2008; 55:391-398.
86. Shamsuzzoha M, Rahman MS, Ahmed MM, Islam AK. Antifertility effect in mice of medicinal plant of the family Acanthaceae. Lancet. 1978;2:900.
87. Shamsuzzoha M, Rahman MS, Ahmed MM. Antifertility activity of a medicinal plant of the genus Andrographis Wall (family Acanthaceae). Part II. Bangladesh Med Res Counc Bull. 1979;5:14-18.
88. Zoha MS, Hussain AH, Choudhury SA. Antifertility effect of *Andrographis paniculata* in mice. Bangladesh Med Res Counc Bull. 1989;15:34-37.
89. Akbarsha MA, Manivannan B, Hamid KS, Vijayan B. Anti-fertility effect of *Andrographis paniculata* (Nees) in male albino rats. Indian J Exp Biol. 1990;28:421-426.
90. Akbarsha MA, Murugaian P. Aspects of the male reproductive toxicity/male antifertility property of andrographolide in albino rats: Effect on the testes and the cauda epididymidal spermatozoa. Phytother Res. 2000;14:432-435.
91. Burgos RA, Caballero EE, Sanchez NS, et al. Testicular toxicity assessment of *Andrographis paniculata* dried extract in rats. J Ethnopharmacol. 1997;58:219-224.
92. Panossian A, Kochikian A, Gabrielian E, et al. Effect of *Andrographis paniculata* extract on progesterone in blood plasma of pregnant rats. Phytomedicine. 1999;6:157-161.
93. Burgos RA, Aguila MJ, Santiesteban ET, et al. *Andrographis paniculata (Ness)* induces relaxation of the uterus by blocking voltage-operated calcium channels and inhibits Ca(+2) influx. Phytother Res. 2001;15:235-239.
94. Mkrtchyan A, Panosyan V, Panossian A, et al. A phase I clinical study of *Andrographis paniculata* fixed combination Kan Jang versus ginseng and valerian on the semen quality of healthy male subjects. Phytomedicine. 2005;12:403-409.
95. Kamlikitkul V, Dechatiwongse T, Tuntawiroon M, et al. Efficacy of *Andrographis paniculata*, Nees for pharyngotonsillitis in adults. J Med Assoc Thai. 1991;74:437-442.
96. Cáceres DD, Hancke JL, Burgos RA, et al. Use of visual analogue scale measurements (VAS) to assess the effectiveness of standardized *Andrographis paniculata* extract SHA-10 in reducing the symptoms of common cold. Phytomedicine. 1999;6:217-223.
97. Melchior J, Spasov AA, Ostrovskij OV, et al. Double-blind, placebo-controlled pilot and phase III study of activity of standardized *Andrographis paniculata* Herba Nees extract fixed combination (Kan Jang) in the treatment of uncomplicated upper-respiratory tract infection. Phytomedicine. 2000;7:341-350.
98. Gabrielian ES, Shukarian AK, Goukasova GI, et al. A double-blind, placebo-controlled study of *Andrographis paniculata* fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis. Phytomedicine. 2002; 9:589-597.
99. Spasov AA, Ostrovskij OV, Chernikov MV, Wikman G. Comparative controlled study of *Andrographis paniculata* fixed combination, Kan Jang, and an Echinacea preparation as adjuvant, in the treatment of uncomplicated respiratory disease in children. Phytother Res. 2004;18:47-53.
100. Poolsup N, Suthisisang C, Prathanturarug S, et al. *Andrographis paniculata* in the

symptomatic treatment of uncomplicated upper respiratory tract infection: A systematic review of randomized controlled trials. J Clin Pharm Ther. 2004;29:37-45.

101. Coon JT, Ernst E. *Andrographis paniculata* in the treatment of upper respiratory tract infections: A systematic review of safety and efficacy. Planta Med. 2004;70:293-298.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/106050