



Acute and subacute toxicity profile of ethanolic stem bark extract of *Albizia coriaria* Welw. ex Oliv. in Wistar albino rats

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ABSTRACT

Albizia coriaria (Fabaceae) crude extracts are key ingredients of several licensed and unlicensed herbal products in East Africa. However, there is limited and often contradicting information regarding its toxicity. We therefore evaluated the acute and subacute toxicity of the ethanolic stem bark extract of *A. coriaria* in mature healthy Wistar albino rats following Lorke's method and OECD guidelines 407. The LD₅₀ of the ethanolic stem bark extract of *A. coriaria* was 2000 mg/kg. The acute toxicity signs observed included piloerection, hyperventilation, lethargy, and loss of righting reflex. There was a significant increase in aspartate aminotransferase, alkaline phosphatase, red blood cells and haemoglobin in rats after 28 days at the dose of 500 mg/kg. Histological analyses revealed multifocal random parenchymal necrosis and scattered periportal mononuclear inflammatory cells infiltration in the liver, interstitial nephritis in the kidney and multifocal lymphoid accumulation in the peribronchiolar and perivascular lung tissue at 500 mg/kg. The ethanolic stem bark of *A. coriaria* was therefore moderately toxic to the rats when administered in a single high oral dose within 24 h. The extract caused a dose dependent toxicity with significant damage to the kidney, liver and lung tissues at a dose of 500 mg/kg after 28 days. Herbal medicines containing *A. coriaria* extracts should be consumed cautiously due to likelihood of toxicity particularly at higher doses greater than 500 mg/kg.

1. Introduction

Traditional and complementary medicine (TCM) is an integral component of Uganda's health care system with over 60 % of the population relying on it for primary health care [41]. However, there are unresolved debates about the quality, safety and efficacy of several TCM

in the country with some reported instances of toxicity and even death being attributed to TCM use [3,14]. The toxicity of TCM could be attributed to presence of inherent toxic phytochemicals from poisonous plants used, contamination during the harvesting, preparation and distribution process, misidentification of the plant species and adulteration [29]. Although there is a general belief that traditional medicines are

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more vigilant when licensing and monitoring *A. coriaria* containing products.

Ethics approval

The protocol for this study was reviewed and approved by Cure Children's Hospital Uganda -Research and Ethics Committee (CCHU-REC/11/020) and registered by the Uganda National Council of Science and Technology (HS1222ES).

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Samuel Baker Obakiro reports financial support was provided by Government of Uganda through the Presidential Scientific Initiative on Epidemics.

Data availability

Data will be made available on request.

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References

- [1] S. Aniagu, F. Nwinyi, D. Akumka, Toxicity studies in rats fed nature cure bitters, *Afr. J. Biotechnol.* 4 (January) (2005) 72–78, <http://www.ajol.info/index.php/ajb/article/view/15055>.
- [2] G. Anywar, E. Kakudidi, R. Byamukama, J. Mukonzo, A. Schubert, H. Oryem-Origa, Indigenous traditional knowledge of medicinal plants used by herbalists in treating opportunistic infections among people living with HIV/AIDS in Uganda, *J. Ethnopharmacol.* 246 (112205) (2020) 1–13, <https://doi.org/10.1016/j.jep.2019.112205>.
- [3] G. Anywar, E. Kakudidi, R. Byamukama, J. Mukonzo, A. Schubert, H. Oryem-Origa, C. Jassoy, A review of the toxicity and phytochemistry of medicinal plant species used by herbalists in treating people living with HIV/AIDS in Uganda, *Front. Pharmacol.* 12 (April) (2021) 1–10, <https://doi.org/10.3389/fphar.2021.615147>.
- [4] G.U. Anywar, E. Kakudidi, H. Oryem-origa, Cytotoxicity of medicinal plant species used by traditional healers in treating people suffering from HIV / AIDS in Uganda, *Front. Toxicol.* 4 (May) (2022) 1–8, <https://doi.org/10.3389/ftox.2022.832780>.
- [5] U.O. Arunsi, G.C. Chinyere, K.O. Ngwogu, A.C. Ngwogu, O.C. Atasié, U.A. Oti, J. K. Akojuobi, C. Udeogu, C. Ibe, Evaluation of the biochemical, haematological and histopathological parameters of female Wistar rats fed with aqueous and ethanol extracts of *Aspilia africana* leaves, *J. HerbMed Pharmacol.* 9 (3) (2020) 257–267, <https://doi.org/10.34172/jhp.2020.33>.
- [6] S. Asgary, G. Naderi, M. Askari, Protective effect of flavonoids against red blood cell hemolysis by free radicals, *Exp. Cardiol.* 10 (2) (2005) 88–90.
- [7] B.J. Auerbach, S.J. Reynolds, M. Lamorde, C. Merry, C. Kukunda-Byobona, P. Ocama, A.S. Semeere, A. Ndyanabo, I. Boaz, V. Kiggundu, F. Nalugoda, R. H. Gray, M.J. Wawer, D.L. Thomas, G.D. Kirk, T.C. Quinn, L. Stabinski, Traditional herbal medicine use associated with liver fibrosis in rural Rakai, Uganda, *PLoS ONE* 7 (11) (2012) 5–12, <https://doi.org/10.1371/journal.pone.0041737>.
- [8] E.O. Awe, S.O. Banjoko, Biochemical and haematological assessment of toxic effects of the leaf ethanol extract of *Petroselinum crispum* (Mill) Nyman ex A.W. Hill (Parsley) in rats, *BMC Complement. Altern. Med.* 13 (2013) 2–7, <https://doi.org/10.1186/1472-6882-13-75>.
- [9] B.S.K. Basile, A.O. Pascal, D.-A. Sanni-yo, Evaluation of acute oral toxicity, hemato-biochemical activity and physiological responses of rabbits and rats administered *Moringa oleifera* leaf extract and meal, *Afr. J. Biochem. Res.* 14 (4) (2020) 142–149, <https://doi.org/10.5897/ajbr2020.1077>.
- [10] R. Byamukama, G. Barbara, J. Namukobe, M. Heydenreich, B. Kiremire, Bioactive compounds in the stem bark of *Albizia coriaria* (Welw. ex Oliver), *Int. J. Biol. Chem. Sci.* 9 (2) (2015) 1013, <https://doi.org/10.4314/ijbcs.v9i2.37>.
- [11] K. Chung, T.Y. Wong, C. Wei, Y. Huang, Y. Lin, K. Chung, T.Y. Wong, C. Wei, Y. Huang, Tannins and human health: a review tannins and human health: a review, *Crit. Rev. Food Sci. Nutr.* 38 (6) (1998) 421–464, <https://doi.org/10.1080/10408699891274273>.
- [12] R.C.B. Cruz, C.D. Meurer, E.J. Silva, C. Schaefer, A.R.S. Santos, A. Bella Cruz, V. Cechinel Filho, Toxicity evaluation of *Cucurbita maxima* seed extract in mice, *Pharm. Biol.* 44 (4) (2006) 301–303, <https://doi.org/10.1080/13880200600715886>.
- [13] D.E.A. de Mendonça, M.A.F. de Godoy, N.C. Lucredi, J.F. Comar, I.V. Almeida, V.E. P. Vicentini, Toxicogenic effects of the mushroom *Ganoderma lucidum* on human liver and kidney tumor cells and peripheral blood lymphocytes, *J. Ethnopharmacol.* 307 (2023) 116226.
- [14] M. Ekor, The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety, *Front. Pharmacol.* (January) (2014) 1–10, <https://doi.org/10.3389/fphar.2013.00177>.
- [15] E.O. Erhirhie, C.P. Ihekwereme, E.E. Ildigwe, Advances in acute toxicity testing: strengths, weaknesses and regulatory acceptance, *Interdiscip. Toxicol.* 11 (1) (2018) 5–12, <https://doi.org/10.2478/intox-2018-0001>.
- [16] J. Fevery, Bilirubin in clinical practice: a review, *Liver Int.* (2008) 592–605, <https://doi.org/10.1111/j.1478-3231.2008.01716.x>.
- [17] B. Kaggwa, E.I. Munanura, H. Kyeiyune, G. Anywar, H. Okella, C.O. Ajayi, R. Wangalwa, J. Mulangwa, C.D. Sesaaizi, L.K. Bagoloire, C.U. Tolo, P.F. Kamba, P. E. Ogwang, Evaluation of catechin, lupeol, and betulinic acid as markers for the chromatographic quality Control of *Albizia coriaria* raw materials; an experimental study, *J. Med. Plants Res.* 17 (5) (2023) 180–200, <https://doi.org/10.5897/JMPR2022.7285>.
- [18] M.M. Kamatenesi, J.G. Ndukui, A. Namutembi, P. Waako, A.B. Karlson, P. Vudriko, Acute and sub-acute toxicity of ethanolic leaf extracts of *Rumex abyssinica* Jacq. (Polygonaceae) and *Mentha pycnantha* L. (Lamiaceae), *Pharmacol. Pharm.* 5 (3) (2014) 309–318, <https://doi.org/10.4236/pp.2014.53038>.
- [19] J.N. Kasolo, G.S. Bimenya, L. Ojok, J.W. Ogwal-Okeng, Sub-acute toxicity evaluation of *Moringa oleifera* leaves aqueous and ethanol extracts in Swiss Albino rats, *Int. J. Med. Plant Res.* 1 (6) (2012) 75–81.
- [20] D.O. Kennedy, E.L. Wightman, Herbal extracts and phytochemicals: plant secondary metabolites and the enhancement of human brain function 1, *Adv. Nutr.* 2 (1) (2011) 32–50, <https://doi.org/10.3945/an.110.000117>.
- [21] E.V.M. Kigundu, G.M. Rukunga, J.M. Keriko, W.K. Tonui, J.W. Gathirwa, P. G. Kirira, B. Irungu, J.M. Ingonga, I.O. Ndiege, Anti-parasitic activity and cytotoxicity of selected medicinal plants from Kenya, *J. Ethnopharmacol.* 123 (3) (2009) 504–509, <https://doi.org/10.1016/j.jep.2009.02.008>.
- [22] C. Kilkenny, W. Browne, I.C. Cuthill, M. Emerson, D.G. Altman, Animal research: Reporting in vivo experiments: The ARRIVE guidelines, *Br. J. Pharmacol.* 160 (7) (2010) 1577–1579, <https://doi.org/10.1111/j.1476-5381.2010.00872.x>.
- [23] K. Kokila, S.D. Priyadarshini, V. Sujatha, Phytopharmacological properties of *Albizia* species: a review, *Int. J. Pharm. Pharm. Sci.* 5 (3) (2013) 70–73.
- [24] Loomis, T., & Hayes, A. (1996). *Loomis's essentials of toxicology* (4th ed.). Academic press.
- [25] M. Mujahid, T. Hussain, H.H. Siddiqui, A. Hussain, Evaluation of hepatoprotective potential of *Erythrina indica* leaves against antitubercular drugs induced hepatotoxicity in experimental rats, *J. Ayurveda Integr. Med.* 8 (1) (2017) 7–12, <https://doi.org/10.1016/j.jaim.2016.10.005>.
- [26] F. Nalimu, J. Oloro, E.L. Peter, P.E. Ogwang, Acute and sub-acute oral toxicity of aqueous whole leaf and green rind extracts of *Aloe vera* in Wistar rats, *BMC Complement. Med. Ther.* 4 (2022) 1–14, <https://doi.org/10.1186/s12906-021-03470-4>.
- [27] J. Namukobe, J.M. Kasenene, B.T. Kiremire, R. Byamukama, M. Kamatenesi-mugisha, S. Krief, V. Dumontet, J.D. Kabasa, Traditional plants used for medicinal purposes by local communities around the Northern sector of Kibale National Park,

- Uganda, *J. Ethnopharmacol.* 136 (1) (2011) 236–245, <https://doi.org/10.1016/j.jep.2011.04.044>.
- [28] O.-P. Note, M.-O. Anne-Claire, T. Miyamoto, T. Paululat, J.-F. Mirjolet, O. Duchamp, D.E. Pegnyemb, M.-A. Lacaille-Dubois, Cytotoxic Acacic Acid Glycosides from the Roots of *Albizia coriaria*, *Nat. Prod.* 72 (10) (2009) 1–6.
- [29] S.B. Obakiro, A. Kiprof, E. Kigundu, I. K'owino, K. Kiyimba, C. Kato Drago, Y. Gavamukulya, Sub-acute toxicity effects of methanolic stem bark extract of *Entada abyssinica* on biochemical, haematological and histopathological parameters in Wistar Albino rats, *Front. Pharmacol.* 12 (September) (2021) 1–9, <https://doi.org/10.3389/fphar.2021.740305>.
- [30] S.B. Obakiro, A. Kiprof, I. Kowino, E. Kigundu, M.P. Odero, T. Omara, L. Bunalema, Ethnobotany, ethnopharmacology and phytochemistry of traditional medicinal plants used in the management of symptoms of tuberculosis in East Africa: a systematic review, *Trop. Med. Health* 48 (68) (2020) 1–21, <https://doi.org/10.1186/s41182-020-00256-1> (2020).
- [31] S.B. Obakiro, A. Kiprof, I. K'owino, M. Andima, R.O. Owor, R. Chacha, E. Kigundu, Phytochemical, cytotoxicity, and antimicrobial activity evaluation of extracts and compounds from the stem bark of *Albizia coriaria* Welw ex. Oliver, *Evid. Based Complement. Altern. Med.* 2022 (2022), <https://doi.org/10.1155/2022/7148511>.
- [32] OECD. (2008). Repeated Dose 28-Day Oral Toxicity Study in Rodents (Issue October).
- [33] B. Oloya, J. Namukobe, W. Ssegooba, M. Afayoa, R. Byamukama, Phytochemical screening, antimicrobial activity and acute toxicity of crude extracts of selected medicinal plant species used locally in the treatment of tuberculosis in Uganda, *Trop. Med. Health* 50 (2022) 16, <https://doi.org/10.1186/s41182-022-00406-7>.
- [34] T. Omara, A. K. V. J, Phytochemicals, polyphenols content, in vitro antioxidant and antibacterial activities of *Albizia coriaria* Welw ex. Oliver flowers, *Tradit. Med. Res.* 8 (2) (2023) 7, <https://doi.org/10.53388/tmr20220531001>.
- [35] T. Omara, A.K. Kiprof, V.J. Kosgei, *Albizia coriaria* Welw ex Oliver: a review of its ethnobotany, phytochemistry and ethnopharmacology, *Adv. Tradit. Med.* (2021) 1–16.
- [36] T. Omara, A.K. Kiprof, V.J. Kosgei, Intraspecific variation of phytochemicals, antioxidant, and antibacterial activities of different solvent extracts of *Albizia coriaria* leaves from some agroecological zones of Uganda, *Hindawi - Evid. Based Complement. Altern. Med.* (2021), <https://doi.org/10.1155/2021/2335454>.
- [37] R. Randrianarivo, R. Razafindrakoto, L.J. Randriamampianina, L. Ramamonjisoa, Toxic effects of seed methanolic extracts of endemic *albizia* species (Fabaceae) from Madagascar on animals, *J. Life Sci.* 8 (8) (2014) 676–689.
- [38] A.L.T. Ribeiro, A.L.B. Shimada, C.B. Hebeda, T.F. de Oliveira, A.P. de Melo Loureiro, W. dos R.P. Filho, A.M. dos A. Santos, W.T. de Lima, S.H.P. Farsky, In vivo hydroquinone exposure alters circulating neutrophil activities and impairs LPS-induced lung inflammation in mice, *Toxicology* 288 (1–3) (2011) 1–7, <https://doi.org/10.1016/j.tox.2011.05.009>.
- [39] F. Schultz, G. Anywar, B. Wack, C.L. Quave, L.A. Garbe, Ethnobotanical study of selected medicinal plants traditionally used in the rural Greater Mpigi region of Uganda, *J. Ethnopharmacol.* 256 (March) (2020) 112742, <https://doi.org/10.1016/j.jep.2020.112742>.
- [40] F. Schultz, O.F. Osuji, B. Wack, G. Anywar, Antiinflammatory medicinal plants from the Ugandan Greater Mpigi Region Act as Potent Inhibitors in the, *Plants* 10 (351) (2021) 1–28.
- [41] J.E. Ssenku, S.A. Okurut, A. Namuli, A. Kudamba, P. Tugume, P. Matovu, G. Wasige, H.M. Kafeero, A. Walusansa, Medicinal plant use, conservation, and the associated traditional knowledge in rural communities in Eastern Uganda, *Trop. Med. Health* 10 (1) (2022), <https://doi.org/10.1186/s41182-022-00428-1>.
- [42] J.R.S. Tabuti, K.A. Lye, S.S. Dhillon, Traditional herbal drugs of Bulamogi, Uganda: Plants, use and administration, *J. Ethnopharmacol.* 88 (1) (2003) 19–44, [https://doi.org/10.1016/S0378-8741\(03\)00161-2](https://doi.org/10.1016/S0378-8741(03)00161-2).
- [43] John R.S. Tabuti, S.B. Obakiro, A. Nabatanzi, G. Anywar, C. Nambejja, M. R. Mutyaba, T. Omara, P. Waako, Medicinal plants used for treatment of malaria by indigenous communities of Tororo District, Eastern Uganda, *Trop. Med. Health* 51 (34) (2023) 1–14, <https://doi.org/10.1186/s41182-023-00526-8>.
- [44] UNCST. (2021). *Uganda National Council of Science and Technology: National Guidelines for Use of Animals in Research and Teaching* (Issue January).
- [45] WHO. (2003). WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants.
- [46] WHO. (2019). WHO Global Report on Traditional and Complementary Medicine.