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MINI REVIEW

An updated review: *Andrographis* species during the pandemic

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Abstract

Among the existence of various medicinal plants, *Andrographis* species caught the attention of many researchers worldwide. Due to its excellent antioxidant properties that are often correlated with powerful pharmacological action, abundant source availability, and low maintenance for cultivation, *Andrographis* species could be considered one of the most promising plant genera that need to be utilized further. This mini-review is aimed to summarize the recent health-related experiments on *Andrographis* species.

1. Introduction

Since the pandemic of COVID-19 has become a global health issue, the habit and awareness of consuming preventive health supplements to maintain our health have increased significantly. Not only supplements that contain synthetic constituents such as vitamins, but medicinal plants have also gotten the spotlight. Even many people that are concerned about the safety of prolonged use of supplements prefer to use natural sources. The preventive and curative natural sources for COVID-19 are still being investigated throughout this time. Interestingly, researchers are not only attracted by plants which generally used as home remedies such as garlic (*Allium sativum*), green tea (*Camellia sinensis*), cinnamon (*Cinnamomum zeylanicum*), turmeric (*Curcuma longa*), lemongrass (*Cymbopogon winterianus*), ginger (*Zingiber officinale*), but also medicinal plants which currently revealed for having antiretroviral properties, namely *Andrographis paniculata*, *Artemisia annua*, *Avicennia officinalis*, and many more (Mahmud *et al.,* 2021; Saha *et al.*, 2021; Nair *et al.*, 2022).

This review discussed *Andrographis* species, which are not limited to the *Andrographis paniculata*. These genera are well-known for their very bitter taste but prominent in pharmacological activities. Varies from snake bites, fever, common cold, dysentery, malaria, diabetes, hypertension, and other diseases are claimed can be cured by their chemical constituents (Dalawai *et al*., 2019). Andrographolide, including its derivatives, and flavonoids are claimed as the responsible constituents for those activities. Ongoing research on this plant has been conducted since years ago and keeps showing satisfactory results. For literary aspects, many publications concerning *Andrographis* species are quite abundant. In 2021, an updated review of *Andrographis paniculata* regarding its microbial activities associated with infectious diseases was published by Hossain *et al.* (2021). Therefore, these are attempts to complement the emerging issue related to COVID-19 and the diverse functions of *Andrographis* species to expose other species as alternative resources.

For resulting high yield of the beneficial constituents from plants extraction method and solvent should be concerned. Flavonoid compounds, which commonly function as antioxidants, could neutralize the excessive oxidative stress inside our bodies and resist the potential of getting infected by diseases. A biochemical reaction is usually used to determine some mechanisms of antioxidant properties. Other than that, the antioxidant is

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frequently correlated with the pharmacological action of plant constituents. In silico, in vitro, and in vivo approaches have been conducted to ensure and confirm the pharmacological action exhibited by the *Andrographis* species. By doing so, the discovery of alternative supportive medicine is expected. Accordingly, this mini-review is expected to recap the recent studies regarding the antioxidant properties and pharmacological activity of *Andrographis* species, precisely during the pandemic.

2. *Andrographis* species and its utilization

2.1 Phytochemical of Andrographis species

Even though there are a lot of *Andrographis* species spread around the world, especially in Asia, the most popular and most utilized is *A. paniculata.* Therefore, a study conducted by Dalawai *et al.* (2019) tried to explore other potential *Andrographis* species that can be counted as alternate sources besides *A. paniculata*. The matured leaves and stem of *A. alata, A. echioides, A. lineata, A. macrobotrys, A. ovata, A. paniculata, A. producta, A. serphyllifolia* were used to evaluate the amount of diterpene lactones (andrographolide, neoandrographolide, and 14-deoxy 11,12 didehydroandrographolide) using the reverse-phase high-performance liquid chromatography (RP-HPLC).

These three kinds of diterpene lactones are varied in the functions of pharmacological activities. Andrographolide is commonly claimed as anticancer and cardioprotective; neoandrographolide is often mentioned as antioxidant, anti-inflammatory, anti-malarial, hepatoprotective, and the 14-deoxy 11,12 didehydroandrographolide is usually claimed as a hypotensive and antiplatelet agent. The result shows that the highest amount of andrographolide is contained in *A. paniculata* leaves (68.35 mg/g DW), followed by *A. lineata* leaves (40.85 mg/g DW), which can be concluded that *A. lineata* is a potential source of andrographolide. *Andrographis macrobotrys* leaves contain the highest amount of neoandrographolide (102.03 mg/g DW) compared to other species, followed by *A. alata* stem (33.21 mg/g DW). 14-deoxy 11,12 didehydroandrographolide is also prominently contained by *A. paniculata* leaves (16.01 mg/g DW), although it is still relatively lower than the andrographolide itself (Dalawai *et al.*, 2019).

Regarding neoandrographolide constituent, a study conducted by Kadapatti and Murthy (2021) claimed *A. alata*, the rare *Andrographis* species distributed mainly in South India, obtained the highest concentration of neoandrographolide (Kadapatti and Murthy, 2021). The result contradicts the study conducted by Dalawai *et al.* (2019), which might occur since various contributing factors could affect the extraction of the chemical constituents contained in plants.

For pharmaceutical matters that usually expect many beneficial constituents, the age of cultivation somehow needs to be considered. Another contributing factor to producing a high yield of expected constituents is the type and concentration of solvents. Kautsar *et al.* (2021) tried to examine the correlation between the *A. paniculata* cultivation ages varying from 2, 3, and 4 months and solvents commonly used for extraction, namely water, 50% ethanol, 70% ethanol, and 100% ethanol. The result shows the 4 months post-planting extracted with 70% ethanol got the highest extraction yield, and the 2 months extracted with water got the lowest extraction yield, 23.37±2.80%, and 16.24±1.83%, respectively. In addition, the UV-Vis and FTIR spectra of the extracts obtained from different ages and solvents show similar profiles but different absorbance intensities. From the results, we can conclude that different cultivation ages and solvents might only affect the yield, not the composition of constituents. The more mature and the more polar solvents would result in a high extraction yield (Kautsar *et al*., 2021).

Another evaluation to explore various *Andrographis* species was conducted by Muralidharan *et al.* (2021). They evaluated *A. echioides* potential by extracting the dried leaves using a Soxhlet apparatus, and ethanol was used as the solvent (Muralidharan *et al.*, 2021). Gurupriya and Catherine (2021) also explored the leaves of *A. echioides* to isolate the constituents using methanolic Soxhlet extraction. Spectral data shows that andrographolide and botulin are found in the isolate (Gurupriya and Catherine, 2021). Another example of *Andrographis* species that is still underexplored is *A. lineata*, which was recently examined by Bhat and Murthy (2021). The dried leaves of *A. lineata* were used for the study, extracted by the Soxhlet apparatus using methanol as the solvent. The andrographolide was targeted to be isolated, and which was previously reported by Dalawai *et al.* (2019) that this species might be the alternative source for andrographolide (Bhat and Murthy, 2021). So, it can be concluded that conventional methods and commonly used solvents are still reliable for extracting the chemical constituents.

2.2 Utilization of Andrographis species for COVID-19

The SARS-CoV-2 virus component responsible for facilitating the entry to the host is the spike glycoprotein that binds to the angiotensin-converting enzyme 2 (ACE 2) of the host cell through the receptor-binding domain (RBD). Another component of SARS-CoV-2 infection is a complex of viral non-structural proteins (NSP)

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responsible for the viral genome replication and transcription, specifically the NSP12. The binding between the Andrographolide to RBD and NSP12 molecules is strongly believed could develop the anti-coronaviral drug candidate. The in-silico approaches conducted by Srikanth and Sarma (2021) show that the dock scores between the andrographolide to RBD and NSP12 are -10.3460, and -10.7313, respectively. These results indicate that andrographolide had a strong affinity and could inhibit the RBD and NSP12, which is a good thing and has the potential to be developed further (Srikanth and Sarma, 2021).

Another study using the *in vitro* approach conducted by Goc *et al*. (2021) tried to compare the binding of SARS-CoV-2 pseudo-virions with some plant extracts that often claimed to occupy a high amount of the phenolic compound and their major components. The study involved tea extracts (85% catechin and 85% theaflavins standardized), epigallocatechin gallate (EGCG), theaflavin, *A. paniculata* extract, andrographolide, liquorice extract, and glycyrrhizic acid. The result showed that the binding percentage of *A. paniculata* extract and the andrographolide is 18.4±1.8 and 22.1±2.5, respectively. The highest binding percentage result is tea extract (85% theaflavins standardized) which gives 100.0±0.3 (Goc *et al*., 2021). This condition shows that specific polyphenols, which are mainly owned by tea, are needed for resulting high binding percentage towards SARS-CoV-2 pseudo-virions.

Instead of andrographolide, Murugan *et al*. (2021) also examined other potential constituents in *A. paniculata*, such as 14-deoxy 11,12 didehydroandrographolide, 14-deoxy andrographolide and neoandrographolide. Hydroxychloroquine, Remdesivir, and Oseltamivir, the commercial drugs for COVID-19 treatment, were used to compare. The computational investigation shows that neoandrographolide has the most potential among the other constituents identified as drug analogues based on the binding free energy data (Murugan *et al*., 2021).

Even though rarely mentioned, bis-andrographolide, the bioactive ligand from *Andrographis* species, could be beneficial for antiviral drug development. A study conducted by Lakshmi *et al*. (2021) investigated the binding between bis-andrographolide and the main protease of SARS-CoV-2 (5R82). The result shows that it has a strong binding affinity to 5R82. Regarding this activity, bis-andrographolide is considered a potential molecule that could block the viral replication of SARS-CoV-2 (Lakshmi *et al*., 2021).

COVID-19 infection might cause an aggressive inflammatory response by releasing a high amount of pro-inflammatory cytokines such as IL-6, IL-18, IL-1β, IFN-γ, TNF-α. In short, this situation is known as a cytokines storm. Severe cytokines storm of COVID-19 patients often leads to fatality, which refers to some vital organ failure. If it is not treated immediately, it could be worse, and the mortality of the patients might be inevitable. In addition, the high NF-*k*B expression is also involved causing the cytokine storm. Andrographolide, as the prominent phytochemical constituent of *A. paniculata*, could reduce the NF-*k*B activation and inflammatory response via regulation of TNF-α trafficking. It is claimed could stabilize the T helper (Th), specifically on Th1, Th2, Th17 responses, then simultaneously could balance the cytokines expression that occurs in cytokines storm (Wang *et al*., 2021; Murugan *et al*., 2021).

Some kinds of medication should be taken for COVID-19 patients with mild to severe symptoms. Headache and fever are examples of the common symptoms related to this virus. Hence, analgesics and antipyretics should be taken to overcome the symptoms. Andrographolide is known for its pharmacological activities, including as an analgesic and antipyretic. The latest experiment related to these activities was conducted on the animal model (in vivo) using a tablet dosage form. The tablet was derived from *A. paniculata* ethyl acetate fraction (AS201-01), which contains an equivalent of 35 mg andrographolide per tablet. Analgesic activity was determined using an acetic acid-induced writhing test on adult male mice, and antipyretic activity was determined by monitoring the rectal temperature within 4 hours after the pyrexia-induced. The result shows that 50 mg andrographolide/body weight could reduce 66.73% of writhing response, and 100 mg andrographolide/body weight after the third hour of administration gave the most satisfactory result antipyretic (Ilmi *et al*., 2021). From several result studies mentioned above, the verdict regarding COVID-19 and its symptoms is that *Andrographis* species could be supplementary-supportive therapy even though it still needs to be examined further to ensure its efficacy and safety.

2.3 Antioxidant properties and miscellaneous utilization of Andrographis species

Another alternative with affordable and more practical ways to get the beneficial phytochemical constituents of *A. paniculata* is infusing the dry leaves with hot water (brewing) to make tea. An experiment conducted by Fitrasyah *et al*. (2021) used the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method to determine the antioxidant activity of *A. paniculata* tea. The result shows that the best formula

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had strong antioxidant activity regarding its IC_{50} (94.0 µg/mL) (Fitrasyah *et al*., 2021). Along with *A. paniculata*, there is *A. producta* that is endemic to Western Ghats, India. A study conducted by Dalawai and Murthy, 2021 investigated the antioxidant activity of *A. producta* stem using in vitro DPPH radical scavenging and Ferric Reducing Antioxidant Power (FRAP) assay. Ascorbic acid and Butylated Hydroxyanisole (BHA) were used as the standard for both assays. The results show that the antioxidant capacities were comparable to standards (Dalawai and Murthy, 2021).

Tajai *et al*. (2021) examined the correlation between constituents contained in *A. paniculata* towards mutagenic Paraquat-induced mammalian cells (AS52). The mutagenic effect might result in DNA damage caused by oxidative stress, which the antioxidant properties can inhibit. In addition, it could be a potential treatment for Paraquat poisoning (Tajai *et al*., 2021). Faisal *et al*. (2021) investigated the cytotoxicity of *A. paniculata* crude extracts with various solvents such as water, methanol, ethanol, dichloromethane, ethyl acetate, and hexane. The dichloromethane crude extract exhibits the most potent cytotoxicity on colorectal cancer cells SW-620, breast cancer cells Michigan Cancer Foundation-7, and ovarian cancer cells A2780 (Faisal *et al*., 2021). Xu *et al.* (2021) study stated that *A. paniculata* polysaccharides could inhibit the proliferation and induce apoptosis of human retinoblastoma Y79 cells. Mechanisms that might involve the upregulation of the capcase-3, capcase-8, capcase-9 expression, and the downregulation of CDK1, cyclinB1 expression (Xu *et al.*, 2021).

Another health problem facing the hardship to control is malaria, caused by the human malarial parasite *Plasmodium falciparum*. The commercial drugs for malaria treatment are mainly derived from medicinal plants. Dwivedi *et al*. (2021) tried the *in vitro* approach for developing *A. paniculata* as the new anti-malarial drug, specifically the *A. paniculata* chloroform extract. The diterpenoid compound contained in the extract shows potential anti-malarial activity even though it needs to be purified and analyzed further for drug development (Dwivedi *et al*., 2021).

A study conducted by Nayak *et al*. (2021) investigated the ability of *A. paniculata* methanolic extract to combat the envenomation by the Indian spectacled cobra, *Naja naja*. The evaluation consisted of how the extract could reverse the hemostatic abnormalities, including activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) in citrated plasma. Drastic reduction of anti-snake venom by 70% shows that the extract can combat the hemostatic abnormalities induced by the *Naja naja* venom (Nayak *et al*., 2021).

Along with abundant biodiversity, the utilization of medicinal plants in Indonesia is becoming a local wisdom legacy. Panjaitan *et al*. (2021) conducted a study of the medical ethnobiology approach to overcome jaundice, a common manifestation of liver dysfunction, that has been done by the Chinese, Dayak, and Malays Ethnics in West Kalimantan, Indonesia. The study shows that the root of *A. paniculata* is used to treat jaundice, specifically in Sambas Regency (Panjaitan *et al*., 2021). These study outcomes show that this species has been worthwhile since years ago and could be considered one of the multi-functional species that ever existed.

4. Conclusion

Alongside *A. paniculata,* other *Andrographis* species, *i.e*., *A. alata, A. echioides, A. lineata, A. macrobotrys, A. ovata, A. producta, A. serphyllifolia*, are worth to be explored and utilized further, especially during this pandemic. They own various and abundant beneficial constituents, such as andrographolide, its derivatives, and flavonoids.

Conflict of interest

The authors declare there is no conflict of interest.

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