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Literature Review of COVID-19 Antivirus Activities Bioactive Compounds and Herbal Plant Extracts

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Abstrack

Introduction: *Currently the world is being hit by a virus outbreak that causes symptoms of pneumonia, on December 31, 2019 China reported a mysterious case of pneumonia with no known cause.* ***Objective:*** *The purpose of this study was to look at bioactive compounds and extracts that have the potential as COVID-19 antivirals.* ***Method:*** *This research is a literature study derived from the PubMed and Science Direct databases using the Preparred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) method.* ***Result and Discussion:*** *In the results of the literature review, 22 articles were found that entered the inclusion criteria. The average extracts and compounds in pre-clinical data showed a very strong IC50 value with a value of <50 ug/ml, while in clinical trials, herbal plant products showed that they were anti-inflammatory and immunomodulatory.* ***Conclusion:*** *So, it can be concluded that natural product products from herbal plants have the potential as an antiviral for COVID-19.*

Keywords: COVID-19; Antiviral; Herbal Plant; Bioactive; Extract;

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Introduction

Currently the world is being hit by a virus outbreak that causes symptoms of pneumonia, on December 31, 2019 China reported a mysterious case of pnemunio of unknown cause. (Mclntosh, 2020). In Indonesia, the first COVID-19 case was found on March 2, 2020, with two cases found (Purnamasari &; Raharyani, 2020)**.**

According to the data *World Health Organization* (WHO), confirmed COVID-19 cases since 2019 to date range from 240,269,449 ((WHO), 2021). Meanwhile, the positive cases of COVID-19 in Indonesia in the latest data on October 18, 2021 were 5,289,414, recovered 146,798, died around 4,593,185 (Ministry of Health of the Republic of Indonesia, 2021). In connection with government policy in tackling the COVID-19 outbreak, the government has issued a decree of the Minister of Health Number HK.01.07/MENKES/104/2020 concerning the determination of corona virus infection as a type of disease that can cause outbreaks and efforts to overcome it (Mufida *et al*., 2020).

In an effort to overcome the COVID-19 outbreak, several treatment approaches have been taken. One of them is by trying to find compounds from herbal plants that have the potential to suppress the COVID-19 virus. Herbal plants have long been known to be effective in treating and dealing with various diseases including COVID-19 (Rachmat Faisal Syamsu, Siska Nuryanti, Arafat, 2021).

Research has been conducted on active compounds from herbal plants against corona antivirals both in pre-clinical trials (in vivo, in vitro) and clinical trials that are useful in the treatment of the COVID-19 virus. Examples include secondary metabolite compounds, namely alkaloids, flavonoids, terpenoids and steroids derived from natural products in herbal plants that can be prime candidates as antivirals for COVID-19 (Ramanathan *et al*., 2020).

So in this case, researchers are also interested in conducting *a literature review* by looking at the potential compounds and mechanisms of these herbal plants that inhibit COVID-19 antivirals into a summary. Which is expected with this thesis can be a guideline and add insight for readers in drug discovery and development.

Therefore, based on the description above, it can inspire researchers to raise it in a thesis entitled COVID-19 Antiviral Activity of Natural Herbal Plant Products (Bioactive Compounds and Extracts).

Method

This research is a literature study derived from journals indexed on Medline through the PubMed and Science Direct portals using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) method. The sample used is an international article or journal that shows the antiviral activity of Corona from Natural Herbal Plant Products (Bioactive Compounds and Extracts) which presents IC50 data that meets the following inclusion criteria. Entire article discussing extracts and compounds that have antiviral activity of COVID-19

a. Inclusion Criteria
   1. International article discussing extracts and compounds that have antiviral COVID-19 with publication year from 2019-2022
   2. The data presented are IC50 value barrier data of extracts and compounds along with clinical trial data

b. Exclusion Criteria
   1. Article does not discuss inhibition of COVID-19 antiviral extracts and compounds
   2. Not COVID-19 antiviral research.

Data Analysis and Processing

The article data obtained is used as basic data and entered in a worksheet table, then the data is analyzed descriptively.

Results and Discussion

Table 1

List of Extracts and Compounds That Have the Potential to Be Antiviral for COVID-19

No	Test Samples	Virus	Result	Mechanism	Reference
1.	Ekstrak Methanol *Gunnera Perpensa L.*	SARS-CoV-2	(IC50) < 0,001 ug/mL	Interfering with RBD ACE2 interaction	(Invernizzi et al., 2022)
2.	Ekstrak Methanol Malva Sylvestris	SARS-CoV-2	IC50 DPPH = 22,11 ug/ml IC50 NO = 19,01 ug/mL	Has NADPH anti-oxidant inhibitory power against 6LU7	(Irfan et al., 2021)
3.	Ethanol Extract 70% Ginko Biloba	SARS-CoV-2 3 CLpro	IC50= 6,68 ug/mL	Gingkolic acid and sciadopitysin can bind to target enzymes	(Xiong et al., 2020)
4.	RevX Products (fermented sorghum)	SARS-CoV-2 Mpro	solid fraction IC_{50} 2.07-0.38 ug/ml	Inhibits the activity of SARS-CoV-2 Mpro	(Chou et al., 2022)
5.	Lantana Camara Ethanol Extract	SARS-CoV-2	IC50 Leaves 3.18 ug/ml IC50 *Fruit* 3,67 ug/ml	Inhibits RdRp gene expression	(Darwish *et al*., 2022)
6.	Water extracts of Camelia Sinensis and Haritaki	SARS-CoV-2	IC50 Green Tea=8.9 g/ml IC50 Teh Haritaki = 8,8 ug/ml.	Blocks viral replication inside cells	(Upadhyay et al., 2020)
7.	Water extract of Perilla leaves	SARS-CoV-2	IC50= 0,12 ug/mL	Inhibits virus replication	(Tang et al., 2021)
8.	ArtemisiaAnnua L leaf extract	SARS-CoV-2	DCM IC50 = <12 M water infusion IC50= 11.8 M	Inhibits SARS-CoV-2 infection	(Nair et al., 2021)
9.	80% Sambucus Nigra ethanol extract	SARS-CoV-2	Interest (IC50 = 0.532 $mg^{/ml-1}$)	Provides resistance to the binding of ACE2 and RBD.	(Boroduske et al., 2021)
10.	Cuphnea Ignea leaf extract	SARS-CoV-2	DMSO IC50 = 2,471 ng/ml	Inhibits the internalization of SARS-CoV-2 by binding to receptors (ACE 2)	(Mahmoud et al., 2021)
11.	Andrographis Paniculata methanol extract	SARS-CoV-2	Gen E IC50 = 1.18µg/ml Gen N IC50 = 1.16µg/ml	Inhibits SARS-COV-2 replication	(Latha et al., 2022)
12.	Ethanol extract 70% Pomegranate bark	SARS-CoV-2	PoPeX $IC_{extract\ 50= 0.06\ mg/ml,}$	Weakens the ability to bind SARS-CoV-2 S-glycoprotein to the ACE2 receptor	(Suručić et al., 2021)
13.	Bosenberg Rotunda Ethanol Extract	SARS-CoV-2	IC50=3,62 ug/mL	Suppresses SARS CoV2 infectivity in Vero E6 cells	(Kanjanasirirat *et al.*, 2020)
14.	Curcumin	SARS-CoV-2	IC50 = 7.8 µg/mL	Inhibits SARS-	(Bormann et al.,

				CoV-2 infection in both Vero E6 cell lines	2021)
15.	Glycyrrhetinic acid dan	SARS-CoV-2	IC50= 3.17 uM	Inhibits SARS-CoV-2 infection by affecting virus entry and replication.	(Yi et al., 2022)
16	licorice-saponin	SARS-CoV-2	IC50= 0.075 uM	Inhibits SARS-CoV-2 infection by affecting virus entry and replication.	(Yi et al., 2022)
17	Dioscin	SARS-CoV-2	IC50 1,5625 mM	Binding to the spike protein of the virus.	(Chen et al., 2022)
18	Celastrol	SARS-CoV-2	IC50 = 0,9866 mM	Binding to the spike protein of the virus.	(Chen et al., 2022)
19	EGCG	SARS-CoV-3CL pro	IC50= 13,9μM	Binding proten 3CL pro	(Bahun et al., 2022)
20	asam ellagic	SARS-CoV-3CL pro	IC50 = 11.8μM	Binding proten 3CL pro	Bahun et al., 2022)
21	resveratro	SARS-CoV-3CL pro	IC50 = 16.9μM	Binding proten 3CL pro	Bahun et al., 2022)
22	Dithymoquinone	SARS-CoV-2	IC50 23,15 ng/ml	It binds to spike and envelopeproteins from SARSCoV-19	(Esharkawy *et al.*, 2022)

Zona Perpensa L.

As the medicinal plant Gunnera perpensa L. is being used by some traditional South African healers for the management of SARS-CoV-2/COVID-19, It was previously reported that the plant contains chemical constituents that inhibit RBD-ACE2 interactions (Cock & Van Vuuren, 2020). In the study of Invernizi et al., (2022) using the AlphaScreen-based protein interaction test showed DCM: MeOH extract from G. Perpensa easily interferes with RBD interaction (USA-WA1/2020)-ACE2 with half-maximum inhibitory concentration (IC_{50}) < 0.001 g/mL, compared to IC_{50} = 0.025 g/mL for antibody neutralizing control REGN 10987 (Invernizzi et al., 2022). DCM: MeOH extracts were analyzed using UPLC-IMS-HRMS to identify the active compound. The monoisotopic mass and molecular formula correspond to [MH]− the quasi-molecular ions of punicalin (C34H22HAI22) and [M-2H]2−the double-charged quasi-molecular ions of punicalagin (C48H28HAI30) with masses of 2.0 ppm and 4.8 ppm (Invernizzi et al., 2022).

Malva Sylvestris

Mallow belongs to the genus malva which contains 100 species and is distributed in Europe, North Africa and Southwest Asia. According to other studies, crude extract of Malva sylvestris is widely screened for anti-HIV bioassays using epithelial lines and blood cells (Benso et al., 2021). In Irfan et al.'s study, (2021) Malva sylvestris dichloromethane extract showed antiradical activity against DPPH and NO radical compounds with radical scavenging (RSA) activity of 88.52 and 91.05% with IC values$_{50}$ 22.11 and 19.01 g/ml. Dichloromethane extract was found to contain high bioactive phytochemicals, which may be related to enhanced antioxidant potential. In-vitro antioxidant results revealed that dichloromethane extract was effective at cooling DPPH and NO. For the first time, through a molecular docking approach, inhibition of these plant phytochemicals with NADPH was noted to exhibit antioxidant behavior to explore anti-SARS-CoV-2 using protease core protein (6LU7) (Irfan et al., 2021).

Ginkgo Biloba

The Girl's Hair Tree is one of the medicinal plants originating from China. According to other studies ginkgolic acid and sciadoptysin isolated from extracts showed strong inhibitory activity against 3CL pro, with IC values$_{50}$ less than 2 M (Perricone et al., 2020). In the research of Xiong et al., (2020) screening of the inhibitory potential of eighty herbal products on the SARS-CoV-2 3CL pro virus has been carried out, the results of Ginkgo Biloba leaf extract are the strongest inhibitory proactivity, namely ($IC_{50= 6.68\ g/mL)}$. Inhibition tests showed that ginkgolic acid and bioflavones isolated from GBLE extract showed relatively strong inhibitory proactivity against SARS-CoV2 3CL, namely ($IC_{50<10\ AD)}$. On test molecular docking simulations clearly show that ginkgolic acid (GA) and sciadopitysin strongly inhibit SARS-CoV-2 3CLpro through reversible and mixed inhibition means (Xiong et al., 2020).

Sorghum

RevX solution extract (trademark Revolutrx INC.) is a fermented extract of sorghum obtained by a unique extraction technology. Previously, this product has been used as an adjunct treatment for lung adenocarcinoma (Al Juhaimi et al., 2018) . In research conducted by Chou et al., (2022) the solid fraction of RevX showed the most effective Mpro inhibitory activity among others with IC_{50} 2.07 g/mL. Molecular tethering of sterol-like components in the RevX extract identified by molecular docking showed that three sterol-like molecules from the RevX extract had overall overlap with the GC376 active cavity that could bind to the active region of the GC376-Mpro complex (Chou et al., 2022). So that the significant capabilities of RevX can provide the possibility of alternative supportive treatment for COVID-19 patients.

Lantana Camara L

Lantana camara has been studied to treat several viral diseases, as in other studies showing the inhibitory effect of leaves against influenza A/Puerto Rico/8/34 (PR8) viruses (Sena Filho et al., 2009). In the study of Darwish et al., (2022) leaves and flowers of L. camara cv Chelsea Gem extract, L. camara cv Spreading sunset flower extract and L. camara cv Drap d'or flower extract showed the most promising inhibitors for COVID-19 virus plaques showing the value of each IC_{50} 3.18, 3.67, 4.18 and 5.01 g/mL. Molecular docking tests of active compounds showing mechanisms of inhibition of RdRp gene expression revealed that isoverbascoside, luteolin-7,4'-O-diglucoside, camarolic acid and lantoic acid showed the highest docking scores of 11,378, 10.64, 6.72 and 6.07 kcal/mol, when compared to remdesivir (5.75 kcal/mol) (Darwish *et al*., 2022). So that these four compounds can be promising candidates for anti-COVID-19 compounds.

Camelia sinensis & Terminalia Chebula

Plant extracts (Green Tea and Haritaki) have been recognized as potential therapeutic options for infection management (Carneiro et al., 2016). Researchers Upadhyay et al., (2020) screened about 51 medicinal plants and found that Tea (Camellia sinensis) and Haritaki (Terminalia chebula) have potential against SARS-COV-2 3CLpro, with IC_{50} for Green Tea at 8.9 g/ml and Haritaki at 8.8 g/ml. In-silico studies suggest that Thearubigins binds cysteine from the active site of proteases and can be pharmacoactive molecules. In addition, other molecules such as quercetin-3-Orutinoside present in tea, were shown to form extensive hydrogen bonds with residues from pockets of active sites (Upadhyay et al., 2020).

Perilla Frutescens Var Crispa

Shiso leaf extract derived from traditional Chinese medicine (TCM) is commonly used to lower heat, and increase endurance. In the study of Tang et al., (2021) an investigation was carried out on the mechanism underlying the anti-SARS-CoV-2 activity of perilla leaf extract using standardized herbal preparations. Perila extract has

IC inhibitory value$_{50}$ 0.12 mg/ in Vero E6 cells. In time-trial drug addition to identify the stage where PLE inhibits the viral replication cycle. PLE showed stronger inhibitory activity when added at an earlier point in time; these findings suggest that PLE plays a role in blocking virus entry (Tang et al., 2021).

Artemisia Annua L

The medicinal plant Artemisia Annua L. is famous for treating various diseases associated with fever, especially malaria (Hsu, 2006). In the study of Nair et al., (2021) DCM extract from Artemisiam annua L. showed anti-SARS-CoV-2 activity with IC values$_{50}$ 12 M and hot water extract of Artemisia anna L show IC_{50} 11.8 A.D. In contrast, artemisinin, when tested as a single drug had an approximate IC_{50} about six times larger (70 M) (Nair et al., 2021). In addition, other studies have shown that both artemisinin and Artemisia extract can reduce levels of inflammatory cytokines including IL-6 and TNF-α in vivo tests (Desrosiers et al., 2020). So it can be concluded that Artimisia annua L. extract has a combination of other active compounds besides artemisinin that block viral infections at the downstream step of viral entry.

Sambucus nigra L

Elderberry has been shown to reduce symptoms of respiratory distress during influenza infection (Tiralongo et al., 2016). In the study of Boroduske et al., (2021) elderberry fruit extract on SARS-CoV2-RBD-ACE2 protein binding in vitro using the ELISA test revealed wild elderberry fruit extract showed an IC50 value of 1.66 mg ml−1 dry extract. While ELISA test results in IC wild elderberry flower extract$_{50}$ Estimated 0.532 mg of dry extract ml−1. The antiviral properties of elderberry have previously been attributed to specific flavonoids belonging to the class of flavonols - 5,7,3',4'-tetra- O-methylquercetin (Boroduske et al., 2021).

Cuphea ignea

Cigar plants belong to the family Lythraceae which are considered an important source of unique natural ingredients for the development of medicines. In the research of Mahmoud et al., (2021) in vitro tests of both Cuphea ignea extract DMSO solution and Cuphea ignea formulation self nano emulsion fying (showing IC value$_{50}$ which is almost the same 2.471 and 2.46 g/ml g/mL. It should be noted that there are safety concerns regarding the use of DMSO as a solvent for which drugs will be administered. So it is necessary to do in vivo tests and other dissolving methods due to the reported toxic effects of DMSO (Hassan et al., 2019). In molecular docking analysis carried out on several compounds in the extract against the main protease of SARS-CoV-2, including rutin, myricetin-3-HAI-rhamnoside and rosmarini acid described the most promising antiviral activity by having the best binding score to the main protease of SARS-CoV-2 with values of 9.28, 7.86, and − 7.05 kcal / mol (Mahmoud et al., 2021)

Andrographis paniculata

Sambiloto is a medicinal plant commonly used in Asian countries to treat symptoms of the common cold (Saxena et al., 2010). In the study of Latha et al., (2022) has evaluated the anti-SARS-CoV-2 activity of androgphis paniculata methanol extract. Flash chromatographic fractionation of crude MeOH extracts from A. paniculata has led to two fractions of different polarities at different RTs. The HPLC fraction obtained at a retention time of 6.5 minutes has shown a corresponding peak of 463m/z in the MS spectrum has confirmed the presence of andrographidine C in A. paniculata MeOH extract. On the determination of in vitro IC tests$_{50}$ for gene E and gene N, Remdesivir shows IC$_{50}$ 0.15μM and 0.11μM, for gene E and gene N androghphis extract shows IC$_{50}$ 1.18μg dan 1.16μg (Latha et al., 2022). Therefore, it was concluded that andrographidine C in the extract may interact with the RdRp of SARS-CoV-2 and may be responsible for the anti-SARS-CoV-2 activity.

Pomegranate

Pomegranate peel is a rich source of bioactive polyphenols that have been known for their beneficial effects on health. In the study of Suručić et al., (2021) the anti-SARS-CoV-2 activity of PoPEx with the main polyphenol measured by HPLC, showed that phenols derived from PoPEx in principle consist of punicalagin isomers (45.57 mg / g DW) while the second most ellagitanin is punicalin (31.31 mg / g BB. IC in vitro resistance test results$_{50}$ calculated from pomegranate peel extract and punicalin compounds around 0.06 mg / mL and puniclagin 0.14 mg / ml. In the concentration range tested, the highest inhibitory activity for glycoprotein-ACE2 S receptor binding interaction was 83.25%, noted for punicalin samples (1 mg/mL). Previous molecular docking studies revealed that punicalin has the highest docking score (- 9.25 kcal/mol) therefore may be a potential candidate to prevent the process of internalization of the virus into host cells (Puttaswamy et al., 2020).

Bonserbeg Rotunda

Fingerroot belongs to the ginger family (Zingiberaceae). The use of traditional Thai herbs, especially their phytochemicals, has been reported to have broad-spectrum activity as anticancer and antiviral (Chusri et al., 2015). In the study of Kanjanasirirat et al., 2020 bosenberg Rotunda extract and panduratin A showed strong antiviral efficacy in Vero E6 cells when treatment was carried out after SARS-CoV-2 infection, with IC$_{50}$ the optimal range is around 3.62 g/mL for Bosenberg Rotunda extract and 0.81 M for panduratin compound (Kanjanasirirat et al., 2020). So Panduratin A compounds can be suggested as a single therapy, and as combination therapy with other FDA-approved agents for effective treatment of COVID-19.

Curcuma Longa

Turmeric has a long history as a medicine for various uses around the world which was previously introduced from China as an antiseptic and anti-inflammatory. In

the study of Bormann et al., (2021) it was reported that turmeric and its bioactive ingredient curcumin can inhibit SARSCoV-2 CPE with IC_{50} of 7.8μg/mL from infected Vero E6 cells. Previous in silico studies have shown that curcumin may interfere with the binding of the spike(S) glycoprotein SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE-2) receptors (Manoharan et al., 2020). More recently, in silico studies predict that curcumin binds strongly to the receptor-binding domain (RBD) of the S-protein, the ACE-2 receptor, and the complex between RBD and ACE-2 (Bormann et al., 2021).

Licorice

Licorice (licorice, Gan-Cao) is the most commonly used Chinese herbal medicine (top 1 among 179 herbs) (Luo et al., 2020). The main compound glycyrrhizic acid has been previously reported to have antiviral activity against H1N1 and SARSCoV influenza viruses (Ji et al., 2016). In the study of Yi et al., (2021) has screened 125 licorice compounds by molecular docking attracting glycyrrhetinic acid, 3-HAI-b-Dglucuronosyl-glycyrrhetinic acid, and licorice-saponins showing much higher affinity than glycyrrhizic acid, which has been reported as an inhibitor of SARS-CoV-2. The potency of the compound was further evaluated by ELISA, SPR, luciferase assay, and antiviral assay and the results were triterpenoids potentially inhibiting SARS-CoV-2 infection, with IC_{50} from 0.075 uM and 3.17mM (Yi et al., 2022) .

Dioscin and Celastrol

Compounds from natural products are known for a long time to have great potential in the discovery and development of medical science. In Chen et al.'s 2022 study, it was reported that there were 39 natural products that targeted the viral receptor-binding domain (RBD) of the SARS-CoV-2 spike protein in in silico analysis. In the ITC binding test to dioscin, celastrol, saicosaponin C, epimedin C, torvoside K, and amentoflavones showed dissociation constants (Kd) of 0.468 mM, 1.712 mM, 6.650 mM, 2.86 mM, 3.761 mM and 4.27 mM, respectively. In cell viability, torvoside K, epimedin, amentoflavones, and saicosaponin C exhibit IC_{50} > 100 mM while dioscin and celastrol each exhibit IC_{50} 1.5625 mM and 0.9866 mM (Chen et al., 2022). So it can be said that these natural products, especially celastrol and dioscin senlife, can bind to the spike protein of the virus and prevent SARS-CoV-2 from entering cells.

Polyphenolic Compounds

The abundance of polyphenols in plants that can be utilized makes them an essential component of nutrition to humans (Musman, 2017). According to other studies, polyphenolic compounds have the potential to have high antioxidant activity and can inhibit antiviral activity (Rasouli et al., 2017). In the study of Bahun et al., 2022 there were 19 different polyphenols screened for inhibitory activity against 3CLpro at 10μM, using MCA-AVLQSGFR-Lys (Dnp)-Lys-NH2 synthetic FRET substrate. To determine the concentration required to inhibit 3CLpro must previously be determined

(IC_{50}) in get the result of IC value$_{50}$ for EGCG, ellagic acid, curcumin, resveratrol and quercetin approx. 13.9 μM, 11.8μM, 11.8 μM, 11.9 μM and 23.4 μM (Bahun et al., 2022). So of these five polyphenols that showed the greatest inhibition of SARS-CoV-2 3CLpro in this study, only quercetin and EGCG.

Nigella Sativa

Seeds from *Nigella sativa* known as black cumin or black seed) is widely used in traditional Islamic medicine and for culinary purposes around the world (Ainane et al., 2014). Other studies have revealed that dithimoquinone is relatively safer than hydroxychloroquine (Rohman et al., 2019). In the research of Esharkawy et al., 2022, the results of in vitro studies of dithimoquinone compounds have anti-SARS-CoV-2 activity at concentrations ($IC_{50= 23.15 ng/ml). Manner}$ Its action has not yet been identified, however, molecular docking studies explain that its binding domain to spikes and envelopeproteins of SARSCoV-19, which can inhibit the entry of the virus into host cells and inhibit ion channels (Esharkawy et al., 2022).

Conclusion

Based on the results of searches conducted from several literatures that discuss the antiviral activity of COVID-19 from herbal plants (extracts & Bioactive Compounds), it can be concluded that traditional Chinese herbal therapy is the most widely used with a percentage value of 17%. In addition, pre-clinical research is the most frequently conducted to determine the antiviral activity of COVID-19 extracts and compounds with a percentage of 90%, followed by clinical trials showing a percentage of 9.7%. Then the most potential content in suppressing COVID-19 antivirals is polyphenol compounds with a percentage of 19.5%. This shows that natural products from herbal plants have the potential to be antiviral for COVID-19.

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