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Liriodenine: The Prospect For Covid-19

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Abstract: Until December 13, 2020, the total Covid-19 cases worldwide is 70,476,836 cases and counted 1,599,922 deaths globally since the start of the pandemic. The best medicine for Covid-19 has not been found yet, so this review intended to reveal potency of Liriodenine to overcome and help care for those affected. Liriodenine ($C_{17}H_9NO_3$) along with Quinine and its derivate Chloroquine and hydroxychloroquine are include in the compound of nitrogen-containing group or alkaloid. The main mechanism of its activity of Liriodenine is DNA Topoisomerase I and II inhibitors that have cytotoxic effect on several human cell lines such as A549, NCI-H226, SPC-A-1, NPC-TW01, ECV2 and 7111, KB, HEp‐2, and against gram (+) and (-) bacteria. Review results showed that Topoisomerase Inhibitor posses dual activity that works on both DNA and RNA, so does Liriodenine predict may affect to RNA virus include SARS-CoV-2 strain or 2019-nCoV. The potency of Liriodenine as new agents for Covid-19 diseases is supported by its other activity antifungal, antiplasmodial (such as Plasmodium falciparum), antidiabetic, antioxidant, and anti-inflammatory (Immunomodulatory) activity. Plants-containing Liriodenine in the world is abundant, not limited to Annonaceae, Magnoliaceae, Lauraceae, Menispermaceae, and Rutaceae. So Liriodenine prospective for developing as herbal therapy or single compound for Covid-19 diseases.
Keywords: Covid-19, Liriodenine, DNA Topoisomerase inhibitor, herbal therapy

1. BACKGROUND

Until December 13, 2020, the total Covid-19 cases worldwide is 70,476,836 cases. By WHO region it is confirmed 43% in Americas, 31% in Europe, 16% in South-East Asia, 6% in Eastern Mediterranean, 2% in Africa, and 1% in Western Pacific. The highest number of cases were reported from the United States of America, Brazile, Turkey, India, and the Russian Federation. It was counted 1,599,922 deaths globally since the start of the pandemic. However, as new cases and new deaths continue to rise, all countries' solidarity will be essential in facing this pandemic and ensure fair access to COVID-19 health products. The world's scientists and global health professionals were called by WHO together to forced the research and development process and develop new norms and standards to contain the spread of the coronavirus pandemic and help care for those affected [1].

I intended to share some research results and study the potential of Liriodenine against the current dangerous disease, covid-19. Hopefully, it will be useful for those readers to see what I recommend that Liriodenine has prospects as the agents for Covid-19 diseases because the potential and opportunities exist. It remained proven in the laboratory and developed.

2. METHODS

This review is made from research results of Liriodenine that were published online in many journals. All articles found in Google, Mendeley literature search, Journal website, and Library Genesis: Scientific articles website. Further information on plant species is confirmed in The Plant List Website. Keywords used include but not limited to Corona Virus, SARS-CoV-2, Covid-19, Liriodenine, Alkaloid, DNA Topoisomerase Inhibitor, RNA Polymerase, Anti-virus, RNA Virus, the activity of Liriodenine, antiviral-, toxicity-, anticancer-, isolation-, antiplasmodial-, antibacterial-, antifungal-, and some plants species that contain Liriodenine. Inclusion criteria are research results of Liriodenine based on data needed and keywords, but in the same activity or plant, the recent year is preferred.

3. RESULT AND DISCUSSION

A. The Coronavirus Disease 2019 (Covid-19)

The global pandemic caused by coronavirus diseases since December 2019 (Covid-19) is known related to severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS- CoV), and SARS- CoV-2. Research showed that incubation of this virus need 4–5 days before symptom onset, and continue the symptoms within 11.5 days. The common symptoms of COVID-19 are fever, dry cough, breathing difficulty, pain in the muscle or joint, headache/dizziness, diarrhea, nausea, and the coughing up of blood. These symptoms can be going worst or severe become acute respiratory distress syndrome (ARDS) after around 8–9 days from onset [2].

The ARDS has cause 70% of fatal COVID-19 cases due to respiratory failure. Furthermore, 28% of fatal COVID-19 cases are caused by the immune system in response to the viral infection, and secondary infections can result in a cytokine storm and symptoms of sepsis. In addition, a severe condition of inflammation may affect multi-organ damage leading to organ failure, especially of the cardiac, hepatic, and renal systems. Renal failure has caused death case of most patients with SARS- CoV [2]**.**

B. Drug Management for Covid-19

Until now, a first-line or drug of choice for threat Covid-19 remains unclear. The government and researchers in almost all countries in the world are still working hard to find cures by *in vitro, in vivo,* or clinical study of some drugs. World Health Organization (WHO) said that remdesivir ($C_{27}H_{35}N_6O_8P$), hydroxychloroquine ($C_{18}H_{26}ClN_3O$), lopinavir ($C_{37}H_{48}N_4O_5$)/ritonavir ($C_{37}H_{48}N_6O_5S_2$), and interferon regimens seem to have little or no effect on 28-day mortality or the in-hospital course of COVID-19 among hospitalized patients [3].

Remdesivir is a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV) infection in cultured cells, mice, and nonhuman primate (NHP) models. An *in vitro* study showed that remdesivir inhibits novel coronavirus (2019-nCoV) infection in Vero E6 cells with EC_{90} value 1.76 μM and also active against infection of human liver cancer Huh-7 cells that sensitive to 2019-nCoV. An *in vivo* evaluation of some antiviral drugs showed that two compounds remdesivir and Chloroquine, potently blocked virus infection at low-micromolar concentration and showed high SI. Half-maximal effective concentration (EC50), half cytotoxic concentration (CC50), and selectivity index (SI) for remdesivir and chloroquine respectively are 0.77 μM, > 100 μM, > 129.87 and 1.13 μM, >100 μM, > 88.50 [4].

Remdesivir is currently under clinical development for the treatment of Ebola virus infection. It is an adenosine analog, which incorporates into nascent viral RNA chains and results in premature termination. This drug functioned at a stage post virus entry, which agrees with its putative antiviral mechanism as a nucleotide analog [4].

Chloroquine ($C_{18}H_{26}ClN_3$) is now known to have potential as an antiviral after previously used as an antimalarial and autoimmune disease drug. It is known to block virus infection by increasing the endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV. As an immune-modulating agent, Chloroquine may synergistically enhance its antiviral effect *in vivo*. Chloroquine functioned at both entrances and at post-entry stages of the 2019-nCoV infection in Vero E6 cells. Chloroquine is widely distributed in the whole body, including the lung, after oral administration. The EC90 value of Chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 μM, which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration. For more than 70 years, Chloroquine is known to be a safe drug and cheap, and now it is potentially clinically applicable against the 2019-nCoV [4]**.**

Hydroxychloroquine is an analog of Chloroquine that has fewer concerns about drug-drug interactions. In the previous SARS outbreak, hydroxychloroquine was reported to have anti-SARS-CoV activity *in vitro*. Hydroxychloroquine (EC50=0.72 μM) was found to be more potent than Chloroquine (EC50=5.47μM) *in vitro* to isolated SARS-CoV-2 virus strain or 2019-nCoV, C-Tan-nCoV Wuhan strain 01, propagated in Vero cells. The molecular mechanism of action of Chloroquine and hydroxychloroquine

inhibit the coronavirus through a series of steps. Firstly, the drugs can change the pH at the surface of the cell membrane and, thus, inhibit the fusion of the virus to the cell membrane. It can also inhibit nucleic acid replication, glycosylation of viral proteins, virus assembly, new virus particle transport, virus release, and other processes from achieving its antiviral effects [5].

All antiviral compounds recommended above have a nitrogen atom (N) in their structures. In a natural product, alkaloid is a secondary metabolite that has one or more nitrogen atoms in its structures because biosynthesis derives from amino acids. Some alkaloids have antibacterial, antifungal, or antiviral activities. In many cases, a single alkaloid can exhibit more than one biological function. In addition, some research on alkaloids has been shown that they usually contain more than one active functional group allowing them to interact with several molecular targets [6].

Chloroquine and hydroxychloroquine were produced synthetically from quinine as a lead compound. Quinine is an alkaloid derived from tryptophan that is isolated from Cinchona sp. (Rubiaceae). These compounds have been widely used as antiviral and antimalarial drugs. Its activity is known as DNA intercalation, inhibition of DNA polymerase, and reverse transcriptase [6]. In continuing to find the new agents for Covid-19 Diseases, based on similarity with these compounds, the nitrogen-containing group and DNA as target molecular, Liriodenine has the opportunity and potential as a new anti-covid-19 drug.

C. Liriodenin as DNA Topoisomerase Inhibitor

Liriodenine ($C_{17}H_9NO_3$) an oxo aporphine alkaloid derived from phenylalanine/tyrosine [6]. The yellow crystal-needle of Liriodenine were isolated from *Cempaka kuning* or *Michelia champaca* L. (Magnoliaceae) guided by mechanism-based yeast bioassay with 0,053% yield from methanol extract of bark. By the research, known that Liriodenine is active both as topoisomerase I and II inhibitors. The structure of Liriodenin can be seen in Figure 1[7].

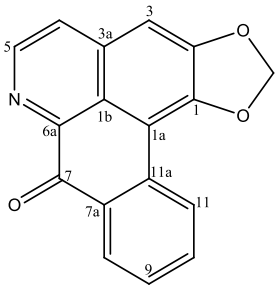

Figure 1. Structure of Liriodenin [7]

DNA topoisomerases are the targets of essential anticancer and antibacterial drugs. Topoisomerases are large proteins or bacterial and eukaryotic enzyme complexes. Topoisomerases are classified as type I (Top1) and type II (Top 2). Type I enzymes cleave one DNA strand at a time and type II both strands to perform their catalytic functions. Both Top1 and Top2 can remove DNA supercoiling. In yeast, the inactivation of Top1 is compensated by the other topoisomerases. However, Top2-deficient yeast strains die at mitosis because Top2 is essential for chromosome condensation and segregation. This is because only Top2 can separate interlinked duplex DNA circles (catenanes). In all cells, decatenation is essential at the end of replication to enable the segregation of newly replicated chromosomes. In anticancer and antibacterial drugs, anti-Top agents or topoisomerase inhibitors stabilizing the cleavage complexes in an open form with a generation of chromosome breaks. This condition becomes cellular toxins poison not only Top2-mediated DNA double-strand breaks (DSB) but also single-strand breaks (SSB), which culminate in cell death [8]**.** In addition to their DNA relaxation activity, topoisomerases are involved in the control of DNA replication and transcription.

As DNA Topoisomerase Inhibitor, Liriodenine has proven active in many cancer cell lines and microbes. The cytotoxicity of Liriodenine in human cell lines was reported by many research in Table 1.

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The mechanism action may be varied and not all fully clear for each cell or type of cancer. The strong activity of Liriodenine to bacteria and fungi can be seen in Table 2.

Table 1. Anti-cancer Related Research of Liriodenine

Liriodenine sources and standard	Methods	Activity	Ref.
Liriodenine, isolated from *Michelia champaca* L. bark	mechanism-based yeast bioassay: *Saccharomyces cerevisiae* strain 1140 (IC12 22.15±1.71 μg/ml), strain 1353 (IC12 24.76±0.56 μg/ml), and strain 1138 (IC12 7.02±1.85 μg/ml)	Topoisomerase I and II inhibitors	[7]
The methanol extract of *Michelia champaca* L. bark	mechanism-based yeast bioassay: *Saccharomyces cerevisiae* strain 1140 (IC12 3424.54±2806.57 μg/ml), strain 1353 (IC12 2124.42±450.40 μg/ml), and strain 1138 (IC12 542.6±102.45 μg/ml)	Topoisomerase I and II inhibitors	[9]
Liriodenine, isolated from *Michelia champaca* L. branches	WST-1 Cell proliferation Assay: A549 human lung adenocarcinoma cells (dose 20 μM, 54.4%) and *MDA-MB-231 human breast adenocarcinoma* cells (dose 20 μM, 51.7%)	Antiproliferative effect	[10]
Liriodenine isolated from *Enicosanthellum pulchrum*	3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl tetrazolium bromide (MTT) Assay: Human ovarian cancer CAOV-3 (IC_{50} 37.3±1.06 μM), human ovarian cancer SKOV-3 (IC_{50} 68.0±1.56 μM), human hepatic WRL-68 (IC_{50} >100 μM), and immortalized human ovarian epithelial cell line SV-40 (IC_{50} >100 μM)	Cytotoxic agent, Inhibits proliferation	[11]
Liriodenin isolated from *Liriodendron Tulipifera* bark	MTT assay: human melanoma A375.S2 (dose100 μM, no data IC_{50}), a Chinese Hamster Ovarian CHO cell line (IC_{50} 8.1±0.1 μg/ml, 29.4±.4 μM)	inhibited the proliferation and cell migration of A375.S2 cells effectively without inducing cell death	[12], [13], [14]
Liriodenine isolated from *Michelia compressa* var. *Formosana* heartwood	MTT Assay: human nasopharyngeal carcinoma NPC-TW01 (IC_{50} 8.99 μM), non-small cell lung carcinoma NCI-H226 (IC_{50} 14.71 μM), T cell leukemia Jurkat (IC_{50} 15.7 μM), renal carcinoma A498 (IC_{50} 4.52 μM), lung carcinoma A549 (IC_{50} 8.82 μM), and fibrosarcoma HT1080 (IC_{50} 9.75 μM)	Cytotoxicity effect	[15]

Liriodenine sources and standard	Methods	Activity	Ref.
Liriodenine isolated from *Michelia compressa* var. *lanyuensis* leaves	Western blotting analysis: human SW480 colorectal cancer cell line, dose 10, 25, and 75 μM	Powerful inhibits colon cancer cell cycle or anti-colon cancer effect	[16]
Liriodenine isolated from *Annona mucosa* leaves	Counting microscopically the number of live parasites using a Neubauer hemocytometer: Leishmania (Leishmania) amazonensis PH8 (IC_{50} 1.43 ± 0.58 μg/mL), Leishmania (Viannia) braziliensis M2903 (IC_{50} 55.92 ± 3.55 μg/mL), BALB/c mice peritoneal macrophages (LC_{50}19.11 ± 1.06 μg/mL)	Antileishmanial activity, Cytotoxic effect	[17]
Liriodenine isolated from *Stephania dinklagei* aerial parts	KB cells (IC_{50} 26.9 ± 2.4 μg/mL)	Cytotoxic effect	[18]
Liriodenine isolated from *Pseuduvaria setosa* (King) J. Sinclair (syn.: *Orophea setosa* King) aerial parts	epidermoid carcinoma KB (IC_{50} 1.2 μg/mL), breast cancer BC (IC_{50} 1.1 μg/mL), a Stimulation index (SI) of lymphocyte proliferation at the nontoxic concentration of μg/mL (SI 0.48 ± 0.02 μg/mL)	strongly cytotoxic and immunomodulating activity	[19]
Liriodenine isolated from the chloroform extract of *Zanthoxylum nitidum* Var. *fastuosum* stems and roots	MTT Assay: Nasopharyngeal carcinoma ECV2 (IC_{50} 17.10 ± 3.76 μM), Nasopharyngeal carcinoma 7111 (IC_{50} 9.676 ± 2.131 μM), Squamous carcinoma Tca8113 (IC_{50} 7.258 ± 3.102 μM), Lung adenocarcinoma SPC-A-1 (IC_{50} 9.814 ± 3.171 μM), Epithelioma KB (IC_{50} 12.60 ± 2.000 μM), Epithelioma KBV200 (IC_{50} 10.18 ± 1.976 μM), Mammary carcinoma MDA-MB-231 (IC_{50} 7.198 ± 0.970 μM), Gastric adenocarcinoma SGC-7901 (IC_{50} 31.97 ± 4.818 μM), Liver cancer BEL7404 (IC_{50} 33.75 ± 3.102 μM), Ovarian carcinoma A2780 (IC_{50} 38.16 ± 4.531 μM), and Cervix carcinoma Hela (IC_{50} 48.47 ± 2.113 μM)	Cytotoxic agent, Inhibits proliferation	[20]
Liriodenin isolated from *Alphonsea elliptica*	Sulforhodamine B (SRB): MCF-7 (IC_{50} 86 μg/mL)	Cytotoxic agent	[21]
Liriodenine isolated from *Mitrephora sirikitiae*	Sulforhodamine B (SRB): murine lymphocytic leukaemia (P-	Cytotoxic agent	[22]

Liriodenine sources and standard	Methods	Activity	Ref.
Weeras., Chalermglin & R.M.K. Saunders	388) (IC_{50} 9.60 ± 0.58 μM), human oral epidermoid carcinoma (KB) (IC_{50} 11.02 ± 0.11 μM), human colon carcinoma (HT-29) (IC_{50} 10.62 ± 0.36 μM), human breast cancer (MCF-7) (IC_{50} 9.20 ± 0.25 μM), human lung carcinoma (A549) (IC_{50} 9.45 ± 0.18 μM), rat glioma (ASK) (IC_{50} 10.65 ± 0.95 μM), and noncancerous human embryonic kidney cell (HEK-293) (IC_{50} 8.07 ± 0.11 μM)		
Liriodenine isolated from varieties plants	Liriodenine inhibits proliferation of lung cancer cells via inhibition of cell cycle progression and induction of apoptosis Liriodenine induces G2/M arrest in A549 cells.	cytotoxicity on A549 cells	[23]
Liriodenin (L)-Platinum Complex: Cis-[PtCl2(L)]	MTT Assay: ECV2 (IC_{50} 4.791 ± 0.427 μM), 7111 (IC_{50} 4.937 ± 0.987 μM), Tca8113 (IC_{50} 4.791 ± 0.617 μM), SPC-A-1 (IC_{50} 3.852 ± 0.494 μM), KB (IC_{50} 3.187 ± 1.460 μM), KBV200 (IC_{50} 13.10 ± 1.497 μM), MDA-MB-231 (IC_{50} 5.730 ± 0.998 μM), SGC-7901 (IC_{50} 4.741 ± 1.686 μM), BEL7404 (IC_{50} 9.155 ± 1.177 μM), A2780 (IC_{50} 7.274 ± 0.580 μM), and Hela (IC_{50} 11.55 ± 2.811 μM)	Cytotoxic agent, Inhibits proliferation	[20]
Liriodenin (L)-Platinum Complex: cis-[PtCl2(L)(DMSO)]	MTT Assay: ECV2 (IC_{50} 6.725 ± 1.725 μM), 7111 (IC_{50} 7.446 ± 1.622 μM), Tca8113 (IC_{50} 6.914 ± 0.624 μM), SPC-A-1 (IC_{50} 10.29 ± 1.344 μM), KB (IC_{50} 12.01 ± 1.569 μM), KBV200 (IC_{50} 8.460 ± 1.822 μM), MDA-MB-231 (IC_{50} 11.19 ± 2.902 μM), SGC-7901 (IC_{50} 7.569 ± 0.559 μM), BEL7404 (IC_{50} 6.908 ± 1.333 μM), A2780 (IC_{50} 21.42 ± 2.166 μM), and Hela (IC_{50} 20.36 ± 2.031 μM)	Cytotoxic agent, Inhibits proliferation	[20]
Liriodenin (L)- **Ruthenium** Complex: cis-[RuCl2(L)(DMSO)2]·1.5H2O	MTT Assay: ECV2 (IC_{50} 10.07 ± 1.980 μM), 7111 (IC_{50} 7.119 ± 1.325 μM), Tca8113 (IC_{50} 6.796 ± 1.228 μM), SPC-A-1 (IC_{50} 7.778 ± 1.954 μM), KB (IC_{50}	Citotoxic agent, Inhibits proliferation	[20]

Liriodenine sources and standard	Methods	Activity	Ref.
	11.86 ± 1.255 μM), KBV200 (IC_{50} 15.29 ± 0.921 μM), MDA-MB-231 (IC_{50} 14.24 ± 1.016 μM), SGC-7901 (IC_{50} 25.98 ± 10.09 μM), BEL7404 (IC_{50} 27.00 ± 8.316 μM), A2780 (IC_{50} 19.64 ± 6.731 μM), and Hela (IC_{50} 30.58 ± 7.173 μM)		
Liriodenine purchased from ChemBest Research Laboratories, Ltd. (Shanghai, China)	MTT Assay: human laryngeal carcinoma HEp‐2 cell line (IC_{50} 2.332 μM)	*Liriodenine induces apoptosis and the inhibition of cell migration in HEp‐2 cells.*	[24]
Camptothecin (standard)	mechanism-based yeast bioassay: *Saccharomyces cerevisiae* strain 1140 (IC12 432.88±140.33 μg/ml), strain 1353 (IC12 2828.99±494.43 μg/ml), and strain 1138 (IC12 95.58±53.04 μg/ml)	Topoisomerase I inhibitor and topoisomerase II inhibitor	[9]
Paclitaxel (standard)	MTT Assay: CAOV-3 (IC_{50} 0.91±0.01 μM), SKOV-3 (IC_{50} 5.5±0.31 μM), WRL-68 (IC_{50} >30 μM), and SV-40 (IC_{50} >30 μM)	Cytotoxic agent, Inhibits proliferation	[11]
Cisplatin (standard)	MTT Assay: CAOV-3 (IC_{50} 62.81±0.35 μM), SKOV-3 (IC_{50} 66.7±0.42 μM), WRL-68 (IC_{50} >100 μM), SV-40 (IC_{50} >100 μM), Tca8113 (IC_{50} 3.665 ± 0.37 μM), SPC-A-1 (IC_{50} 20.26 ± 2.03 μM), KB (IC_{50} 5.265 ± 0.53 μM), SGC-7901 (IC_{50} 7.96 ± 0.64 μM), BEL7404 (IC_{50} 98.04 ± 17.45 μM), A2780 (IC_{50} 30.20 ± 2.83 μM), and Hela (IC_{50} 38.66 ± 7.55 μM)	Citotoxic agent, Inhibits proliferation	[11], [20]

Table 2. Antibacterial and Antifungal Related Research of Liriodenine

Liriodenine source	Microbes	Activity	Ref.
Liriodenine isolated from *Zanthoxylum tetraspermum*	*Staphylococcus aureus* (Minimum Bactericidal Concentration, MBC 100 μg/ml) *Cladosporium cladosporioides* (area inhibition 150 mm^2 at 2 mg of Concentration), *Cladosporium gloeospori-oides* (area inhibition 100 mm^2 at 2 mg of Concentration)	Moderate Antimicrobial Activity	[25]
Liriodenine isolated from *Pseuduvaria setosa* (King) J.	*Mycobacterium tuberculosis* H37Ra (MIC 12.5 μg/ml)	Antituberculosis activity,	[19]

Liriodenine source	Microbes	Activity	Ref.
Sinclair (syn.: *Orophea setosa* King) aerial parts			
Liriodenine isolated from *Cananga odorata* barks	Area inhibition (mm) at concentration 200 μg/disc: *Bacillus subtilis* (11), *B. Megaterium* (11), *Staphylococcus aureus* (22), *Sarcina lutea* (14), *Streptococcus-β-haemolyticus* (20, MIC 32 μg/ml), *Escherichia coli* (15), *Pseudomonas aeruginosa* (17), *Shigella flexneri* (13), *S. Shiga* (20, MIC 32 μg/ml), *S. Boydii* (15), *S. Dysenteriae* (21), *S. Sonnei* (20), *Salmonella typhi* (22), *Klebsiella species* (24). Area inhibition (mm) at concentration 400 μg/disc: *Aspergillus flavus* (15), *A. Niger* (17), *A. Versicolor* (28), *Candida albicans* (42) cytotoxic activity to Brine Shrimp (LC_{50} 4.89 μg/ml)	Antibacterial, Antifungal and cytotoxic activity	[26]
Liriodenine isolated from *Michelia champaca* L. root barks	Area inhibition (mm) at concentration 10 μg/disc: *Bacillus cereus* (14), *B. Coagulans* (18), *B. Megatarium* (16), *B. Subtilis* (14), *Lactobacillus casei* (16), *Micrococcus luteus* (18), *M. Roseus* (16), *Staphylococcus albus* (16), *S. Aureus* (14), *S. Epidermidis* (12), *Streptococcus faecalis* (14), *St. Pneumoniae* (16), *Agrobacterium tumefaciens* (18), *Citrobacter freundii* (14), *Enterobacter aerogenes* (12), *Escherichia coli* (14), *Klebsiella pneumonia* (18), *Neisseria gonorrhoeae* (12), *Proteus mirabilis* (18), *P. Vulgaris* (14), *Pseudomonas aeruginosa* (16), *Salmonella typhi* (16), *Sa. Typhymurium* (14), *Serratia marcscens* (12), *Trichomonas vaginalis* (18)	Antibacterial activity	[27]
Liriodenine isolated from *Beilschmiedia alloiophylla* (Rusby) Kosterm.	Progressive double dilution method to *Candida albicans* (MIC 16.0 μg/ml)	Anti-fungal	[28]

Splicing is modulating of many gene expressions that are involved in apoptosis regulation. These genes are transcribed as diverse mRNA species, which encode proteins with sometimes opposite functions. The splicing of caspase-2 mRNA can be a specific consequence of topoisomerases I and II poisoning, not always depend on induction of apoptosis. Both Topoisomerase I and II Inhibitors Trigger Exon 9 Inclusion in human leukemic U937 and HeLa Cells. Topoisomerase inhibitors play a negative role in caspase-2L

mRNA assembly and suggest that both topoisomerases' families may be involved in the splicing control of caspase-2 pre-mRNA. Because increased inclusion of caspase-2 exon nine may limit topoisomerase poisons' pro-apoptotic activity, molecules that specifically prevent this effect would theoretically sensitize tumor cells to topoisomerase inhibitors [29].

As Topoisomerase I and II inhibitors, Liriodenine is a powerful antiproliferative agent for colon cancer. The flow cytometry analysis showed that Liriodenine potently inhibited the cell cycle of SW480 cancer cells via the NO- and p53-dependent G1/S phase arrest pathway [16].

Peoples at higher risk for Covid-19 Diseases included people aged 60 years and over and those with underlying medical problems like high blood pressure, heart and lung problems, diabetes, obesity, or cancer. However, anyone can get sick with COVID-19 and become seriously ill or die at any age [3]. Liriodenine has a cytotoxic effect on human lung adenocarcinoma cells A549, non-small cell lung carcinoma NCI-H226, lung adenocarcinoma SPC-A-1, human nasopharyngeal carcinoma NPC-TW01, ECV2 and 7111, human oral epidermoid carcinoma KB, human laryngeal carcinoma HEp‑2 (Table 1). These cancer cell lines related to the respiratory tract predict to be work on symptoms of Covid-19 diseases such as dry cough, sore throat, difficulty breathing, and chest pain because of damage or infection of the lungs organ.

In hospitals, physicians will sometimes use antibiotics to prevent or treat secondary bacterial infections, which can be a complication of Covid-19 in severely ill patients [3]. In this situation, the antibacterial activity of Liriodenine (Table 2) can be beneficial for the patients.

D. Topoisomerase bind/Interact RNA Virus

All fine-tuned steps of key cellular processes such as gene expression, transcription, translation, DNA recombination and repair, epigenetic imprinting, as well as various forms of innate and adaptive immunity, are essentially constituted by natural genetic content operators [30]. There is a unique of the DNA world, that Type IA topoisomerases from all domains of life often possess dual topoisomerase activities for both DNA and RNA and they may solve topological problems for both nucleic acids in all domains of life. In animals, Top3b- TDRD3 is a dual-activity topoisomerase complex that can act on DNA to stimulate transcription and mRNA to promote translation [31] [32].

In animals, one of the 2 Type IA topoisomerases, Top3b, contains an RNA-binding domain, possesses RNA topoisomerase activity, binds mRNAs, interacts with mRNA-binding proteins, and associates with the active mRNA translation machinery. The RNA-binding domain is required for Top3b to bind mRNAs and promote normal neurodevelopment. Top3b forms a highly conserved complex with Tudor-domain-containing 3 (TDRD3), a protein known to interact with translation factors, histones, RNA polymerase II, single-stranded DNA and RNA. Top3b requires TDRD3 for its association with the mRNA translation machinery [31]. This Top3b is required for yellow fever virus and dengue virus-2 replication. The study found that Top3b is required for efficient replication of all positive-sense-single stranded RNA viruses tested, including SARS-CoV-2 or 2019-nCoV. So Top3b is an attractive antiviral target [33].

The study reported that Top3b is a host factor essential for efficient replication of a diverse group of (+) ss RNA viruses. A recombinant chikungunya virus (CHIKV), an alphavirus of the *Togaviridae* family was sensitive to TDRD3 knockout, and coxsackievirus B3 (CVB3), an enterovirus of the family *Picornaviridae*, was dependent on Top3b for efficient replication. Most important in the context of the Covid-19 diseases, four beta coronaviruses, of the *Coronaviridae* family, SARS-CoV, SARS-CoV-2, MERS-CoV, and SCH1014-CoV, a bat coronavirus, were significantly crippled by Top3b [33].

Human diseases causing RNA viruses include Orthomyxoviruses, Hepatitis C Virus (HCV), Ebola disease, SARS, influenza, polio measles and retrovirus, including adult human T-cell lymphotropic virus type 1 (HTLV-1), human immunodeficiency virus (HIV) and now the Covid-19 diseases. RNA viruses have RNA as genetic material, which may be a single-stranded RNA or a double-stranded RNA. The endogenous retroviruses are long-terminal repeat (LTR)-type retroelements that account for approximately 10% of human or murine genomic DNA [30].

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Ebola virus (EBOV), a member of the family *Filoviridae*, in the order *Mononegavirales*, causes a severe hemorrhagic fever in humans and nonhuman primates, with high fatality rates. During the infection of host cells, EBOV proteins must interact with various host proteins for virus replication. A novel cellular factor, DNA topoisomerase 1 (Top1), interacts with Ebola virus (EBOV) protein L (EBOL) and plays important roles in the EBOV life cycle. In the presence of EBOL, Top1 colocalizes and interacts with EBOL in the cytoplasm, where transcription and replication of the EBOV genome occur. So, knockdown of Top1 markedly reduced virus replication and viral polymerase activity. This study also showed that the phosphodiester bridge-cleaving and recombination activities of Top1 are required for the polymerase activity of EBOL [32].

There are reports of inhibition of virus replication by topoisomerase inhibitors. Research showed that the HIV replication in MT-2 cells was inhibited by Coumermycin A1, an inhibitor of DNA gyrase (Top 2), is an antibiotic produced by *Streptomyces* spp. It also has activity against murine retrovirus replication *in vitro* with drug-resistant isolates. Amsacrine and teniposide can inhibit the replication of human cytomegalovirus *in vitro*. Novobiocin and nalidixic acid, active against eukaryotic topoisomerase II as well as prokaryotic DNA gyrase, can inhibit SV40 DNA and RNA synthesis. The inhibition of decatenation of daughter chromosomes and the breakage in replication forms in Cairns structures in SV40 replication by topoisomerase II and I inhibitors, respectively [34].

Topoisomerase I from the vaccinia virus was used to study the mechanism of RNA strand scission that similar to modulate DNA topology. Vaccinia topoisomerase I act catalytically since it is able to turn over during the RNase reaction. During vaccinia topoisomerase-mediated RNA cleavage, greater than 90% of the RNA substrate is typically converted to a 2', 3' cyclic product [35]. This mechanism is illustrated in Figure 2.

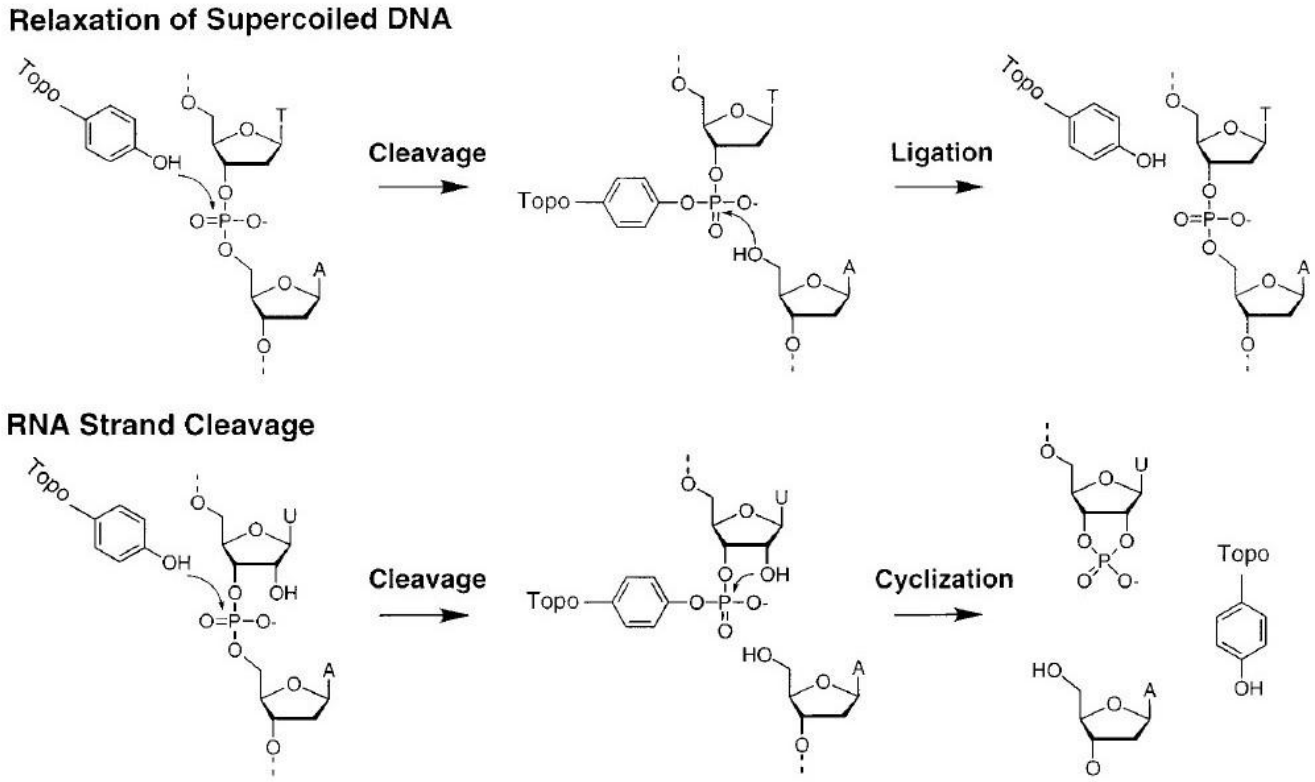

Figure 2. Comparison of Topoisomerase 1-mediated relaxation of supercoiled DNA and RNA strand cleavage [35]

Enterovirus 71 (EV71) is one of the causative agents of hand, foot and mouth disease (HFMD) associated with severe neurological disease. As a member of the Picornaviridae family that includes human pathogens such as poliovirus (PV) and hepatitis A virus, EV71 is a non-enveloped virus with a single, positive-sense RNA genome. Camptothecin, a DNA topoisomerase 1 (Top1) inhibitor, inhibits both viral RNA replication and translation based on luciferase replicon studies. Camptothecin is a limited spectrum antiviral against enteroviruses that functions in a Top1-dependent but cytotoxicity-independent manner. Top1 is, in turn, needed for maximal EV71 viral RNA replication and viral protein synthesis [36]**.**

Topoisomerase I (Top1) and II (Top2) may catalyze distinct steps of hepatitis B virus (HBV) cccDNA synthesis and that pharmacologic targeting of these cellular enzymes may facilitate the cure of chronic hepatitis B. HBV contains a relaxed circular (rc) partially double-stranded DNA (3.2 kb in length) genome but replicates its genomic DNA via reverse transcription of an RNA intermediate called pregenomic RNA (pgRNA).All Top inhibitors significantly reduced HBV cccDNA at concentrations much lower than their maximal noncytotoxic concentrations. Because all of the Top inhibitors examined are mechanistically Top poisons, they freeze Top1 and Top2, covalently attaching to the 3' and 5' ends of cleaved DNA and thus, result in single-strand and double-strand DNA breaks, respectively. It is, therefore, possible that the observed reduction of cccDNA amounts in the Top poisontreated cells is not due to the inhibition of cccDNA synthesis but the result of the cleavage of already formed cccDNA. This mechanism of HBV was studying using Top 2 Doxorubicin, Idarubicin and Top1 Camptothecin, Topotecan [37]**.**

Based on all studies reported above, it is strongly predicted that Liriodenin can also play a role in viral RNA, including SARS-CoV-2 virus strain or 2019-nCoV. In this case, because it is active as a top 1 and top 2 inhibitors in DNA can interact and bind with RNA vise versa. This antiviral potency for Covid-19 also supports by related research of Liriodenine against some parasite or plasmodium causing malaria diseases (Table 3). It may be similar to Quinine derivates such as Chloroquine and Hydroxychloroquine, which is first known as antimalarial drugs.

Table 3. Anti-Plasmodial Related Research of Liriodenine

Liriodenine or other material tested	Methods	Activity	Ref.
Liriodenine isolated from *Liriodendron Tulipifera* bark	Parasite lactate dehydrogenase (pLDH) activity assay to measure parasite viability: chloroquine-sensitive strain (D10) of Plasmodium falciparum (IC_{50} 4.1 ± 1.0 μg/ml, 14.9 ± 3.6 μM), chloroquine resistant strain (Dd2) of Plasmodium falciparum (IC_{50} 7.9 ± 1.1 μg/ml, 28.7 ± 4.0 μM)	Antiplasmodial activity	[14]
Liriodenine isolated from *Glossocalyx brevipes* Benth. leaves	Plasmodial assay: Plasmodium falciparum Indochina (W-2) was resistant to Chloroquine, pyrimethamine, Sulfadoxine, and quinine (IC_{50} 2373 μg/ml, Plasmodium falciparum Sierra (D-6) was resistant to Mefloquine (IC_{50} 1326,30 μg/ml)	Antiplasmodial activity: moderate	[38]
Liriodenine isolated from *Stephania dinklagei* aerial parts	Leishmania donovani promastigotes (IC_{50} 15±0.15 μg/ml), Leishmania donovani Amastigotes (IC_{50} 72.4±1.30 μg/ml, toxic > 30 μg/ml), Trypanosoma brucei brucei (IC_{50} > 30 μg/ml), multidrug-resistant strain of Plasmodium falciparum K1 (IC_{50} 25,1±2,92 μg/ml)	Antiprotozoal activity	[18]

Liriodenine or other material tested	Methods	Activity	Ref.
Liriodenine isolated from *Pseuduvaria setosa* (King) J. sinclair (syn.: Orophea setosa King) aerial parts	multidrug-resistant strain of Plasmodium falciparum K1 (IC_{50} 2.8 μg/ml)	Antimalaria activity,	[19]
Liriodenine isolated from *Pseudomalmea boyacana* J.F. Macbr.) Chatrou	liriodenine exhibited the highest activity against Chloroquine sensitive (F32) and chloroquine resistant (W2) strains of *Plasmodium falciparum* (CI_{50} = 8.0-10.0 μg/ml)	Antiplasmodial activity	[39]
Liriodenine isolated from *Annona foetida* Mart.	177.0 ± 10.6 μg/ml (IC_{50}) to Epimastigote forms; 4.0 ± 0.2 μg/mL (EC50) to Trypomastigote forms	antiparasitic natural products, trypanocidal activity against *Trypanosoma cruzi*	[40]
Mefloquine (standard)	Plasmodial assay: Plasmodium falciparum Indochina (W-2) was resistant to Chloroquine, pyrimethamine, Sulfadoxine, and quinine (IC_{50} 4.78 μg/ml, Plasmodium falciparum Sierra (D-6) was resistant to Mefloquine (IC_{50} 11.67 μg/ml)	Antiplasmodial activity	[38]
Chloroquine diphosphate (Sigma, standard)	Parasite lactate dehydrogenase (pLDH) activity assay to measure parasite viability: chloroquine-sensitive strain (D10) of Plasmodium falciparum (IC_{50} .01 ± .01 μg/ml, .03 ± .01 μM), chloroquine resistant strain (Dd2) of Plasmodium falciparum (IC_{50} .07 ± .01 μg/ml, .23 ± .01 μM) Plasmodium falciparum Indochina (W-2) was resistant to Chloroquine, pyrimethamine, Sulfadoxine, and quinine (IC_{50} 145,30 μg/ml) Plasmodium falciparum Sierra (D-6) was resistant to Mefloquine (IC_{50} 4,77 μg/ml)	Antiplasmodial activity	[14], [38]

E. Others activity of Liriodenine

Liriodenine reported has activity as an antidiabetic agent, acetylcholinesterase inhibitor, antioxidants, regulates dopamine biosynthesis activities, and anti-inflammatory (Immunomodulatory) activity (Table 4). If Liriodenine use as a new agent for Covid-19 diseases so it will give a positive side for some patients with comorbid diseases such diabetes and others related illness.

Table 4. Other Activity Of Liriodenin

No	Liriodenine sources	Activity	Concentration	Ref.
1	Liriodenine isolated from *Tinospora crispa* (L.) Hook. f. & Thomson	Antidiabetic agents, α-glucosidase inhibitor	0.562 ± 0.003 mg/ml (IC_{50})	[41]

No	Liriodenine sources	Activity	Concentration	Ref.
2	Liriodenine isolated from *Beilschmiedia alloiophylla* (Rusby) Kosterm.	Antidiabetic agents, α-glucosidase inhibitor; acetylcholinesterase (AChE) inhibitor; anti-leishmanial against *Leishmania donovani* LV9	45.4± 0.5 µM (IC_{50}); 3.5± 1.0 µM (IC_{50}); 30.2± 2.0 5-10 µM (IC_{50})	[28]
3	Liriodenine isolated from *Alphonsea elliptica* (Annonaceae)	Antioxidant activity, DPPH free radicals scavenging assays; inhibition of xanthine oxidase (XO)	AO (% I at 500 µg/mL) 10.73±0.45; XO 7.66 µg/mL	[21]
4	Liriodenine by the Korea Research Institute of Chemical Technology	Liriodenine regulates dopamine biosynthesis by partially reducing TH activity and TH gene expression and has protective effects against L-DOPA-induced cytotoxicity in PC12 cells. Lidodenine was not cytotoxic toward PC12 cells at concentrations up to 20 µM. At concentrations higher than 30 µM, liriodenine exhibited cytotoxic effects through an apoptotic process	Liriodenine IC_{50} value 8.4 µM.	[42]
5	Liriodenine isolated from *Liriodendron chinensis* leaves	anti-inflammatory (Immunomodulatory) activity	*Nitric oxide generation assay:* The content of nitric oxide (NO) from peritoneal macrophages of rats induced by ipopolysaccharide (LPS) are 20.48 ± 1.01, 21.58 ± 1.08, and 17.55 ± 0.84 µg/ml at concentration of 1, 10, and 100 µg/ml, respectively. MTT Assay: The proliferation index (PI) of T lymphocytes cells are 1.475 ± 0.119, 1.186 ± 0.095, and 1.915 ± 0.501 at concentration of	[43]

No	Liriodenine sources	Activity	Concentration	Ref.
			1, 10, and 100 µg/ml, respectively.	

F. Liriodenine resources

Liriodenine has been isolated in many plant species; among them were Annonaceae, Magnoliaceae, Lauraceae, Menispermaceae, and Rutaceae. Annonaceae belongs to 128 genera and include 5,130 scientific plant names of species. Magnoliaceae belongs to 6 genera and include 1000 scientific plant names of species. Lauraceae belongs to 68 genera and include 7,537 scientific plant names of species. Menispermaceae belongs to 68 genera and include 1,670 scientific plant names of species. Rutaceae belongs to 158 genera and include 6.686 scientific plant names of species [44]. This data shows the possible abundance of plants-containing Liriodenine in the world and very supportive if it develops as a new agent for Covid-19 diseases. Detail of some plants part and percentage of yield in some plants can be seen in Table 5.

Table 5. Liriodenin resources

No	Plants Species/Families	Plants Part	Yields of Liriodenin isolate (%)	Ref.
1	*Enicosanthellum pulchrum* (King) Heusden (Annonaceae)	Rooth	8 mg of 1.96 g ethyl acetate extract (0.4%)	[11]
2	*Alphonsea elliptica* (Annonaceae)	Bark	6.1 mg of 25 g dichloromethane extract (0.0244%)	[21]
3	*Annona diversifolia* (Annonaceae)	Radicle/root	102.2-112.6 µg/g of dried material (radicle stage); 378.3-778.3 µg/g of dried material (seedling stage)	[45]
4	*Annona diversifolia* (Annonaceae)	stems	7.1-130.2 µg/g of dried material (radicle stage); 64.55-181.9 µg/g of dried material (seedling stage)	[45]
5	*Annona foetida* Mart. (Annonaceae)	Branches	17 mg of 9.2 g CH_2Cl_2 extract (0.1845 %)	[40]
6	*Annona mucosa* Jacq. [synonym *Rollinia mucosa* (Jacq.) Baill].	Leaves	10 mg of 11.2 g of dichloromethane extract (0.0893%)	[17]
7	*Annona salzmannii* (Annonaceae)	Leaves	5.8 mg of 65 g methanol extract (0.0089%)	[46]
8	*Annona vepretorum* (Annonaceae)	Leaves	1.5 mg of 112 g methanol extract (0.0013)	[46]
9	*Beilschmiedia alloiophylla* (Rusby) Kosterm. (Lauraceae)	Bark	5 mg of 3 g crude alkaloid extract (0.1%)	[28]
10	*Cananga odorata* Hook. F. and Thom. (Annonaceae)	Leaves	10 mg of 175.9 g methanol extract (0.0057%)	[47]
11	*Cleistopholis patens* (Benth.) Engl. & Diels (Annonaceae)	Root bark	34 mg of 3.85 kg dried root bark (0.00088%)	[48]
12	*Glossocalyx brevipes* Benth.	Leaves	20 mg of 6 g methylene chloride fraction (alkaloid amterial) (0.3333%)	[38]
13	*Goniothalamus tapis* Miq.	Bark	3 mg of 157.6 g methanol extract	[49]

No	Plants Species/Families	Plants Part	Yields of Liriodenin isolate (%)	Ref.
	(Annonaceae)		(0.0019%)	
14	*Goniothalamus uvaroides* King (Annonaceae)	Bark	10 mg of 54.1 g methanol extract (0.0185%)	[49]
15	*Liriodendron chinensis* (Hemsl.)Sarg. (Magnoliaceae)	leaves	5 mg of 80 g alcohol 95% extract (0.0063%)	[43]
16	*Liriodendron tulipifera* (Magnoliaceae)	stems	36 mg of 187.5 g methanol extract (0.0192%)	[13]
17	Magnolia grandiflora L. (Magnoliaceae)	leaves	4 mg of 1.8 kg leaves (0,0002%)	[50]
18	*Michelia champaca* L. (Magnoliaceae)	Bark	30.2 mg of 10.21 g active fraction (0,2958% active fraction or 0.053% of methanol extract)	[7]
19	*Michelia champaca* L. (Magnoliaceae)	Stems	14.5 mg of 25 g ethanol extract (0.058%)	[51]
20	*Michelia champaca* L. (Magnoliaceae)	Stems	8 mg of 231.8 g methanol extract (0.0035%)	[52]
21	*Michelia champaca* L. (Magnoliaceae)	Branches	12.53 mg of 181.5 g methanol extract (0.0069%)	[10]
22	*Michelia compressa* var. *Formosana* (Magnoliaceae)	Heartwood	379 mg of 720 g ethanol extract (0.0526%)	[15]
23	*Michelia compressa* var. *Lanyuensis* (Magnoliaceae)	Leaves	39 mg of 73.8 g CHCl3-soluble fraction (0.0528%)	[16]
24	*Michelia floribunda* Finet & Gagnep. (Magnoliaceae)	Stem barks	195 mg of 4.4 kg dried stem barks (0.0044%)	[53]
25	*Mitrephora sirikitiae* Weeras., Chalermglin & R.M.K. Saunders (Annonaceae)	Leaves and stems	13.9 mg of 90 g crude MeOH leaf extract (0.0154%), and 12.4 mg of 60 g crude MeOH extract of stems	[22]
26	*Polyalthia cauliflora* var. *Cauliflora* (Annonaceae)	Stem barks	1.3 mg of 16.25 g crude methanol extract (0.008%)	[54]
27	*Polyalthia longifolia* var. *pendula* (Annonaceae)	Leaves	11 mg of 550 mg crude alkaloid part from 50.2 g chloroform fraction (0.022 %)	[55]
28	*Pseudomalmea boyacana* (J.F. Macbr.) Chatrou (Annonaceae)	Aerial parts	Isolation from 3.1 g alkaloid fraction	[39]
29	*Pseuduvaria setosa* (King) J. Sinclair [syn.: *Orophea setosa* King] (Annonaceae)	Aerial parts	6.7 mg of 3.6 g CHCl3 fraction (0,1861%) or 0.0289% of ethanol 95% exctract	[19]
30	*Stephania dinklagei* Diels (Menispermae)	Aerial parts	8.2 mg of 2 g methanol extract (0,41%)	[18]
31	*Stephania dielsiana* Y.C. Wu (Menispermaceae)	Roots	5 mg of 45 g ethanol 95% extract (0.0111 %)	[56]
32	*Tinospora crispa* (L.) Hook. f. & Thomson (Menispermaceae)	dried T. crispa vines	3.5 mg of 25 g Fraction D (0,014 %)	[41]

No	Plants Species/Families	Plants Part	Yields of Liriodenin isolate (%)	Ref.
33	*Zanthoxylum caudatum* (Rutaceae)	Stem barks	2.47 g of 21.5 g CHCl3 extract (11.4884%)	[25]
34	*Zanthoxylum nitidum* Var. *fastuosum* (Rutaceae)	Stems and Roots	0.11% basing on dry plantweight. It was crystallized from the chloroform part and re-crystallized in chloroform for purification	[20]
35	*Zanthoxylum tetraspermum* Wight and Art. (Rutaceae)	Stem barks	400 mg of 69 g light petroleum extract (0.5797%)	[25]

4. CONCLUSIONS

Liriodenine ($C_{17}H_9NO_3$), along with Quinine and its derivate Chloroquine and hydroxychloroquine, are include in the compound of nitrogen-containing group or alkaloid. The main mechanism of its activity of Liriodenine is DNA Topoisomerase I and II inhibitors that have a cytotoxic effect on several human cell lines such as A549, NCI-H226, SPC-A-1, NPC-TW01, ECV2 and 7111, KB, HEp‑2, and against gram (+) and (-) bacteria. This literature review also showed that Topoisomerase Inhibitor posses dual activity that works on both DNA and RNA, so does Liriodenine predict may affect to RNA virus include SARS-CoV-2 strain or 2019-nCoV. The potency of Liriodenine as a new agent for Covid-19 diseases is supported by its other activity antifungal, antiplasmodial, antidiabetic, antioxidant, and anti-inflammatory (Immunomodulatory) activity. Plants-containing Liriodenine in the world is abundant, not limited to Annonaceae, Magnoliaceae, Lauraceae, Menispermaceae, and Rutaceae.

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