International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Special Issue 5, 2022

Review Article

NATURAL PLANT REMEDIES FOR DEPRESSION DURING THE COVID-19 PANDEMIC, UPDATE REVIEW

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Received: 24 Sep 2022, Revised and Accepted: 09 Nov 2022

ABSTRACT

COVID-19 is disease caused by SARS-CoV-2 virus which was first discovered in Wuhan, China on the end of 2019. The COVID-19 pandemic generates many sufferers to experience symptoms of depression. Natural plant has been used for a long time for various ailments, including depression. This literature review aims to describe various types of plants and their mechanisms that can be used to help deal with symptoms of depression during the COVID-19 pandemic. This article was compiled by conducting a literature search using the keywords "covid-19", "depression", and "natural products" on PubMed, Scopus and Cochrane Library engine searching and followed the inclusion criteria, namely, the maximum literature publications from the last 10 y in English and discuss natural products that can be used to help overcome depression during the covid-19 pandemic. We found that thirteen medicinal plants are noteworthy to be considered as antidepressant drug candidates. The medicinal compounds need to be developed furthermore in the future since Covid-19 pandemic is not over yet. These plants have established the molecular mechanism to remedies depression and hopefully can be alternatives medicine to treat depression that have mild side effects compared to synthetic drugs.

Keywords: COVID-19, Depression, Natural plant

DOI: https://dx.doi.org/10.22159/ijap.2022.v14s5.18 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

At the end of 2019, the world was shocked by an incident that made many people worried, namely the emergence of the SARS-CoV-2 virus which causes Coronavirus disease (COVID-19) [1]. This incident began in Wuhan, Hubei Province, China. This virus attacks the respiratory system with mild to severe symptoms and can even cause death [2]. COVID-19 is spread in 231 countries with the highest prevalence in Europe. As of May 13, 2022, there were 520 912 257 million confirmed cases of Covid-19, with a total death toll of 6 272 408 million worldwide [3].

When SARS-CoV-2 enters the cell through binding with Angiotensin 2 Converting Enzyme (ACE2) on the cell surface [4], its viral RNA will be expressed into the cytoplasm and the replication starts to produce new particles of SARS-CoV-2. This phenomenon leads to the cell death and the movement of the virus to infect other cells [5] as ACE2 has massive numbers on every different cell surface such as cardiomyocyte, endothelial cells, central nervous system (neurons and glia cells). The penetration of the virus is not only supported by its capability to attach with the receptor, a mediator that is produced during the early stage of infection, for example, IL-6 that facilitates more microbes to penetrate through the blood-brain barrier [6, 7]. In the central nervous system's cells, this impairment is manifested to some neural symptoms such as anxiety, headache, and depression [8, 9]. The interpretation of nervous disorders can be seen when respiratory symptoms appear and sometime after recovering from Covid-19 [10].

Depression is a common mental disease worldwide, with an estimated 3.8% of the population suffering from depression, i.e. 5.0% of adults and 5.7% of adults older than 60 y. Around 280 million people in the world suffer from depression [11]. This condition has many factors that are commonly associated with the monoamine hypothesis where there is the reduction of neurotransmitter levels such as serotonin, noradrenalin, and dopamine. This impairment results in neuropsychiatric symptoms [12-14]. Depressive disorders can be experienced by all age groups. The results of Riskesdas 2018 show that depressive disorders have started to occur since the adolescent age range (15-24 y), with a prevalence of 6.2%. The pattern of depression prevalence increases with increasing age, the highest at the age of 75+ years at 8.9%, 65-74 y at 8.0% and 55-64 y at 6.5% [15]. In the first year of the COVID-19 pandemic, the global prevalence of depression and anxiety increased by 25% [16].

With the limited availability and access of conventional medicines, traditional medicines are becoming more desirable due to their increased perception of safety and widespread availability [17]. Currently in developed countries, herbal medicines have been widely developed for medicinal purposes because it is seen from the safety and lower side effects [18]. According to WHO, 80% of the population in developing countries have used herbal medicine for the treatment of their disease, and 85% of the herbal medicines used are of plant origin [19].

A number of synthetic drugs used as standard treatment for clinically depressed patients have side effects that can compromise therapeutic treatment. Common side effects include digestive or respiratory problems, cardiac arrhythmias, anxiety, dry mouth, drowsiness, fatigue, and agitation. Some drug-drug interactions may also occur [20]. To overcome the side effects caused by synthetic and chemical drugs, medicinal plants may be relatively better chosen as alternative treatments because many studies with different models have reported positive pharmacological effects of plants in the treatment of depression [21].

Natural compound from the plant has several pharmacological activities such as anti-depression activity, Serotonins compound and another alkaloid shows relevant effect for this activity. One the other hand, herbal medicines used popularly for thousands of years are the clearest source or reference for the application of therapeutically effective medicines [22]. Traditional herbal medicines can consist of a combination of several herbs or single plant application, therefore have a promising candidate for treating depression with high safety [23–27]. The purpose of this review is to describe and investigate the various types of plants that have the potential as antidepressants and their mechanisms during COVID-19.

MATERIALS AND METHODS

This article was compiled by conducting a literature search using the keywords "covid-19", "depression", and "natural products". The literature must fulfill the inclusion criteria, namely, the maximum literature publications from the last 10 y in English and discuss natural products that can be used to help overcome depression

during the covid-19 pandemic. The search results were re-sorted according to the inclusion criteria. Using the PubMed engine searching about 73 articles related by this subject, Scopus engine searching 10 articles and Cochrane library obtain 6 articles related by the research. There were 19 publications that met the inclusion criteria. The number of publications excluded was 70 publications because they did not meet the requirements. We are studied the molecular mechanism of the active compound of the plants to determine the precious effect of the natural product on depression healing.

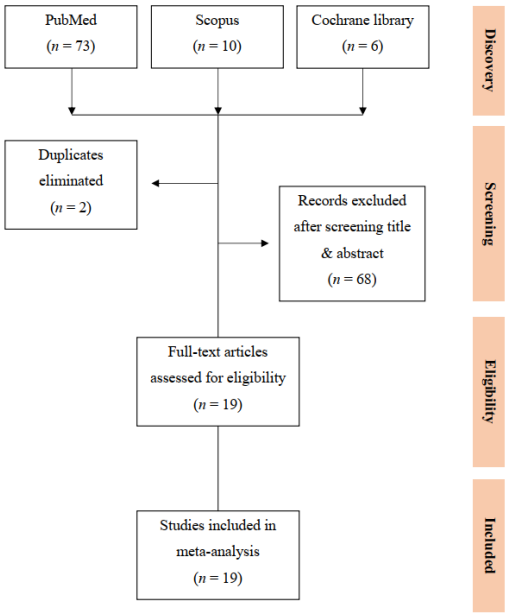

Fig. 1: The runaway step to collect the literature for natural plants remedies during Covid-19 pandemic

Table 1: Various plants followed local name, part of plant, active compound and mechanism of action as anti-depressive agent

No	Plants	Local name	Part of plant	Compounds	Mechanism	Reference
1	*Cinnamomum burmannii*	Cinnamon	Bark	Cinnamaldehyde	Increase serotonin rate in hippocampus	[28, 29]
2	*Withania somnifera*	Ashwagandha	Roots and leaves	Root extracts and withanolide	Antioxidant and serotonergic activity is linked to its antidepressant effect.	[30]
3	*Echium amoneum*	Red feathers	Leaves and flowers	Aqueous extract alkaloids	Increases neurotransmitter levels of dopamine and CSF serotonin	[31, 32]
4	*Agastache mexicana*	Toronjil morano/Toronjil de Casa	Aerial parts and flowers	Tilianin (34).	Binding with GABA/BZD receptor (34).	[33-35]
5	*Bupleurum falcatum*	Chaihu	Roots	Quercetin and luteolin	Regulates the JNK expression in the hippocampus	[36-38]
6	*Crocus sativus* L.	Saffron	Stigma	Crocin, picrocrocin, safranal	Modulates the activity of hMAO-A and hMAO-B enzymes and can act as a very promising hMAO-B inhibitor	[39-41]
7	*Piper nigrum* L.	Black pepper	Fruit	Piperin	Decrease in adrenocorticotropic hormone and levels of corticotropin-releasing hormone, thus modulate the hypothalamic-pituitary-adrenal axis	[42, 43]
8	*Moringa oleifera* L.	Drumstick tree	Leaves	Flavonoids and polyphenolic	Central nervous system oxidative stress reduction comes with its effects on noradrenergic and serotonergic neurotransmission pathways	[44, 45]
9	*Curcuma longa* L.	Turmeric	Rhizome	Curcumin	Inhibit monoamine oxidase (MAO-A and higher doses of MAO-B) and increase the neurotransmitter levels (5-HA and DA) (46)	[46, 47]
10	*Centella asiatica*	Gotu kola	Leaves	Asiaticoside	Increase monoamine neurotransmitter levels and reverses CMS-induced inflammatory cytokine elevations that may be regulated via the cAMP/PKA signaling pathway	[48]
11	*Morinda citrifolia* L.	Noni	Fruit	Scopoletin and rutin	Antidepressant activity mediated by its interaction with α1-and α2-adrenoceptors	[49]
12	*Ocimum basilicum*	Basil	Essential oil from the leaves	Eugenol	Inhibit monoamine oxidase enzyme that plays a role in the metabolism of neurotransmitters, serotonin and norepinephrine	[50]
13	*Zingiber officinale*	Ginger	Rhizome	Dehydrozingerone	Inhibit MAO enzymes which result in increased levels of the neurotransmitters dopamine, serotonin and noradrenaline through the serotonergic and noradrenergic systems (51)	[52]

RESULTS

On this review we conducted a literature study by searching articles related with depression and Covid Pandemic. Covid pandemic are global obstacle, many implications related with the pandemic for example increase depression of life. Study of Covid pathological is mandatory to prevents a lot of affect on daily life of human, include the study of the plant related to Covid remedies particularly related by depression side. We are searching the articles with correlation of Covid and depression, after sorting the literature, information about natural products for depression was collected in the table 1.

DISCUSSION

The rates of depression in the general population could be up to 7 times higher during the COVID-19 pandemic [53]. The rates of depression reported in previous epidemic outbreaks (SARS and Ebola) ranged between 3% and 73.10% [54], which is lower than the rates of depression during the COVID-19 pandemic [53]. Covid pandemic related by depression due to pathologically the SARS-Cov2 virus disturb the homeostasis condition on the brain related with serotonin and another neurotransmitter that affected the mood condition include depression. In addition, the socio-economic impact by COVID also contribute to to increase depression in around the word.

COVID-19 is related to depression since SARS-CoV-2 binding with ACE2 also occurred on the surface of neuron and glia cells in the central nervous system. This impairment is manifested as depression, anxiety, headache, and other neuropsychiatric symptoms [8, 55]. In order to deal with the depression symptoms of COVID-19, there are some ways of therapy needed such as synthetic drugs, which are currently developing, or herbal treatment. The invention of new drugs can be associated and based on the natural products found in some medicinal plants [56].

Synthetic drugs from various types of groups such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), dopamine reuptake inhibitors (DRIs), tetracyclic antidepressants, receptor antagonists serotonin and reuptake inhibitors (SARIs), selective noradrenaline reuptake inhibitors (NTIs), multimodal antidepressants, and melatonergic agonists has been used as pharmacological agents for management of depression [57].

The use of synthetic drugs has side effects such as digestive or respiratory problems, cardiac arrhythmias, anxiety, dry mouth, drowsiness, fatigue, and agitation. Some drug interactions may also occur. This can be an opportunity for medicinal plants to be used as an alternative treatment for depression [20]. Many patients prefer treatment using herbal medicines because synthetic drugs have some side effects that endanger therapeutic treatment [58, 59].

Medicinal plants are believed to be a source of materials that can be used in the development and synthesis of drugs. Some plants are considered as an important source of nutrients so they are recommended for treatment because they have therapeutic value [60].

The use of herbal medicine in dealing with emotional symptoms can improve the quality of life, therefore, it can be used as adjuvant therapy in covid-19 patients with psychological complications [61]. Vary plants above are reported having pharmacological effects on depression.

Cinnamomum burmannii

Cinnamon was used as traditional medicine to alleviate cough, fever, and joint pain [29, 62, 63]. Some studies reported that it has a phenolic compound, cinnamaldehyde, that has anti-inflammatory effects in the hippocampus. This activity allows the number of serotonin to increase which results in the decreased level of mesolimbic dopamine. Reduction of mesolimbic dopamine causes the increment of dopamine in the mesocortical area which leads to increase in mood and alleviate the depression [29].

Withania somnifera (WS)

Antidepressant effect of ashwagandha is associated with its antioxidant properties and serotonergic action [64, 65]. A study suggested that the administration of WS root powder can avoid decrease of serum serotonin levels [66]. Meanwhile, withanolide, a compound found in WS, is attached to human receptors with more prominent affinity than serotonin and Selective Serotonin Reuptake Inhibitor (SSRI) fluoxetine in *in silico* studies (30). Moreover, 240 mg of standardized WS extract administered within two months in randomized study can dramatically reduce depression based on Hamilton Anxiety Rating Scale (HAM-A) [67].

Echium amoneum (EA)

The alteration of CSF serotonin and dopamine were caused by the administration of *Echium amoneum* extract. It increases the serotonin concentration which may escalate social interaction and dominance. Moreover, altered serotonin metabolite, which is cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA) reduction can cause suicide behavior in human. Meanwhile, a study reported that reduction of dopamine production is a cause of depression in schizophrenia [68]. The administration of EA aqueous extract can increase the level of dopamine and potentiates responses to psycho stimulants in the human body [31].

Agastache mexicana (AM)

Medicinal compound found in AM, tilianin, is shown as a possible ligand of GABAA/BZDreceptor. Tilianin is reported having the same hydrophobic exclusive fragment of diazepam, a popular GABAergic agonist and largely prescribed as psychoactive medicine. Therefore, based on a pharmacophoric model, GABAA/BZD receptor but not 5-HT1A receptor is involved [34].

Bupleurum falcatum

The expression of JNK mRNA and p-JNK protein in mice increased significantly and chaihu can control the JNK expression. Chaihu can clearly improve the depressive state of model mice and the mechanism may correlate with regulation JNK expression in the hippocampus [37]. *Bupleurum falcatum* may also affect depression through the hypothalamic corticotropin-releasing factor modulation and regulation of the noradrenergic system in locus coeruleus [69].

Crocus sativus L.

Depression is associated with decreased antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase, and increased oxidative stress markers such as malondialdehyde (MDA) [70]. Saffron and its constituents are powerful antioxidants. Safranal and crocin increase CAT activity in liver tissue [71, 72] and also protected against oxidative stress, by their lowering effects on lipid peroxidation markers such as MDA [73, 74]. Saffron derivatives can modulate the activity of the enzyme hMAO-A which regulates serotonin, epinephrine, and norepinephrine metabolism in catecholaminergic neurons and the enzyme hMAO-B which metabolizes benzylamine and phenethylamine in *substantia nigra.* The two hMAO isoforms take part in dopamine metabolism [40].

Piper nigrum L.

Antioxidant and bioactive compounds of black pepper are very important to improve brain function. Piperine enhances neuroprotection as well as improves cognitive performance. Piperine decreases in adrenocorticotropic hormone and levels of corticotropin-releasing hormone, thus modulating the hypothalamic-pituitary-adrenal axis [42, 43]. *Piper nigrum* indicates antidepressant-like effects through the serotonergic transmission system [75]. Limonene in *piper nigrum* inhibits methamphetamine-induced locomotor activity possibly via dopamine neurotransmission and regulation of 5-HT [76, 77].

Moringa oleifera L.

The mechanism of action of moringa oleifera seems to be partly due to the reduction of CNS oxidative stress accompanied by its effects on serotonergic and noradrenergic neurotransmission pathways. The flavonoid content in *moringa oleifera* also acts as an antioxidant through neurogenesis. Flavonoids and antioxidants help to get rid of

free radicals and neutralize the destructive interaction of free radicals with DNA and cell membranes [44]. High content of saponins in *Moringa oleifera* can also help in antidepressant effects [78].

***Curcuma longa* L.**

Curcuma longa, also known as turmeric is a spice from the *zingiberaceae* family which contains the active compound curcumin that has potential for treatment depression [47]. Curcumin is used in the health and food fields, including as a coloring agent, flavoring and non-toxic additive [79, 80]. The part of the plant used as a therapy is a bright yellow to orange rhizome in the root system [81]. Curcumin not only can inhibit monoamine oxidase (MAO-A and higher doses of MAO-B) but also can regulate levels of NE, DA and 5-HT. Curcumin can increase the neurotransmitter levels (5-HA and DA) in the brain. This indicates that the antidepressant effect of curcumin is related to the monoaminergic system [46].

Centella asiatica

Centella asiatica is a plant from the *Apiaceae* family known as Brahmi or Mandookaparni in Ayurvedic medicine and known as Gotu Kola in Indonesia [82, 83]. *Centella asiatica* contains asiaticoside, triterpenoid compound which has antidepressant properties mediated through activation of the BDNF/tropomyosin receptor kinase B (TrkB) signaling pathway in a chronic mild stress (CMS) rat model [84]. Asiaticosides treatment increases monoamine neurotransmitter levels and reverses CMS-induced inflammatory cytokine elevations that may be regulated via the cAMP/PKA signaling pathway [48]. cAMP/PKA activation has been reported to increase CREB phosphorylation and induce the expression of CRE-regulated genes, such as BDNF. Suppression of CREB signaling in the hippocampus may interfere with the expression of CRE-regulated genes, such as brain-derived neurotrophic factor (BDNF), which play an important role in depression [85].

***Morinda citrifolia* L.**

Morinda citrifolia L. or commonly called noni fruit is a plant from the Rubiaceae family (coffee family) and also know mengkudu in Indonesia and Malaysia [86]. Noni fruit contains nutritional compounds that can treat various diseases in the human body [87]. Noni fruit contains active compounds including rutin (flavonoid) and scopoletin (coumarin derivative) that show antidepressant activity mediated by its interaction with α1-and α2-adrenoceptors [49]. α1-and α2-adrenoceptors plays an important role in regulating the function of the prefrontal cortex (PFC) by modulating the release of noradrenaline (NA) and various other neurotransmitters in the central nervous system (CNS) [88].

Ocimum basilicum

Ocimum basilicum is an aromatic plant from the *Lamiaceae* family originating from South Asia [89]. *Ocimum basilicum* has been reported to be widely used, one of which is in the health sector to treat various diseases since ancient times [90, 91]. This plant contains essential oil as much as 0.04%-0.70%, with eugenol as the dominant compound that have antidepressant effects with mechanism action like antidepressants MAOIs [50, 92]. MAOI inhibits monoamine oxidase enzyme that plays a role in the metabolism of neurotransmitters, serotonin and norepinephrine [50]. MAOIs increase the levels of three neurotransmitters, namely dopamine, norepinephrine, and serotonin in the brain by regulating various aspects of behavior, cognition, motivation, and mood [93].

Zingiber officinale

Zingiber *officinale* or ginger is a rhizome-shaped plant that can be consumed as food, medicine, or herb [94]. Ginger has been used for a long time as an herbal plant to treat various diseases [95]. Dehydrozingerone (DHZ) is an active compound contained in *Zingiber officinale,* which has the potential as an antidepressant through its monoamine oxidase (MAO) inhibitory activity [52]. DHZ exhibits MAO-A inhibition *in silico* and increases levels of the neurotransmitters dopamine, serotonin and noradrenaline in the brain via the serotonergic and noradrenergic systems associated with antidepressant-like effects [51].

CONCLUSION

Covid pandemic induces depression through alter the neurotransmitters homeostasis and possibly by enhance the socio-economic pressure. The therapeutic effects of these thirteen medicinal plants are noteworthy to be considered as antidepressant drug candidates, particularly on Covid condition. The medicinal compounds need to be developed furthermore in the future since Covid-19 pandemic is not over yet despite the molecular mechanism of several compounds established to cure depression condition. In addition, these herbal medicines hopefully can be alternatives medicine to treat depression that has mild side-effects compared to synthetic drugs. These literature review also showed the possible mechanism of action from varies of plants on remedies the depression related with the active compound from each plant.

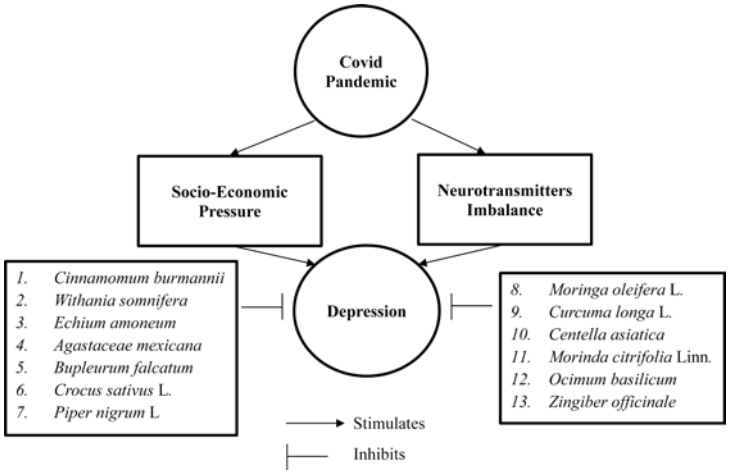

Fig. 2: The Schematic correlation between covid pandemic and depression related by natural plants remedies

ACKNOWLEDGMENT

Thank you to Universitas Padjadjaran for providing APC

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed fairly.

CONFLICT OF INTERESTS

Among the authors have no conflict of interest

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