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The Potential of Indonesian Natural Materials as Immunomodulators and Tonics for National Resilience of Public Health in the Era Covid-19 Pandemic

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Abstract

Indonesia is abundant in natural substances with immunomodulatory and tonic qualities that can help maintain immunity and keep the body healthy in the face of the COVID-19 pandemic. This paper Analysing herbal plants that are effective in terms of safety and actual efficacy in increasing the endurance and fitness of Indonesians in the face of the Covid 19 Pandemic becomes the first step in pioneering efforts to create national drug independence and sovereignty in the context of national health sector resilience. This study suggests that herbal plants such as Papaya (Carica papaya), Turmeric/Curcumin (Curcuma domestica), Meniran (Phyllanthus niruri), Brotowali (Tinospora crispa), and Ginger (Zingiber officinale Rosc.) which have immunomodulatory and tonic properties, as well as data on the potential for increasing endurance and body wellness by enhancing immune response, to raise awareness of the nation's ability and potential natural resources in supporting national drug independence, resilience, and sovereignty. Therefore, the usage of immunomodulator herbal medications is thought to have an activity to boost the immune system and protect the body from COVID-19 and preparedness for the next pandemic. However, these findings should be confirmed through additional scientific research or clinical trials.

Keywords
natural resources; immunomodulator; tonic; pandemic

I. Introduction

From the end of 2019 until now, the world was shocked by the emergence of the Covid 19 Pandemic, which attacked all parts of the sectors globally, starting from economics and public health (Singhal, 2019). SARS Cov 2 is a new virus still in the same family as the viruses that cause SARS and MERS. On March 12, 2020, WHO declared COVID 19 a pandemic (spreading disease to almost all countries). The SARS Cov-2 virus enters the body, binds to the ACE-2 receptor on lung cells through the receptor-binding domain (RBD), then enters the cell (cytoplasm). Then the viral cell proliferates to cause clinical symptoms (Astuti, 2020). Sihombing (2020) state that Covid-19 pandemic caused everyone to behave beyond normal limits as usual. The outbreak of this virus has an impact especially on the economy of a nation and Globally (Ningrum, 2020). The problems posed by the Covid-19 pandemic which have become a global problem have the potential to trigger a new social order or reconstruction (Bara, 2021)

Progress occurs so quickly both clinically, diagnostically, and therapeutically. SARS COV-2 is a virus that spreads from human to human, which although mortality is low (3%) but has high morbidity, within ten months, more than 100 million people have been infected (Lotfi, 2020). Given the very high level of morbidity and the fast spread from human to human, there must be a thought to overcome these problems so that they can be resolved in a complete manner (Keni, 2020).

Given the existence and diversity of Indonesia's Natural Resources (SDA), one of which is medicinal raw material resources from plants which are recorded as the 2nd most enormous biodiversity in the world after Brazil, researchers have a high sense of optimism to be able to take advantage of Indonesia's natural resources as soon as possible. Currently, the available therapeutic strategies to treat SARS COV-2 infection are supportive and preventive therapies to reduce transmission in the community (Cascella, 2021).

II. Review of Literature

At least there are four potential approaches for the application of herbal medicine therapy to fight COVID-19: (a) Consumption of nutritious foods and herbs as supplements to prevent infection and strengthen immunity; b) Use of masks and face shields; (c) use of essential oils as air disinfectants to stop aerosol transmission; and (d) the use of disinfectants as sanitizing agents to provide a clean and infection-free environment (Panyod, 2020). This enormous potential of natural resources should be utilized optimally for the progress of the Indonesian nation and state, especially for the interests of National Defense and Security (hankamneg). Indonesia's defense doctrine, Sishanta (Universal Defense System), which has an archipelago perspective, requires a touch of the nation's generation in the regional logistics readiness to carry out the concept of protracted war (Muradi, 2017). Indonesia's natural potential is the primary source of various types of medicinal plants. In line with the government's program to increase the use of medicinal plants in medicine, the development of Traditional Indonesian Medicines is guaranteed to ensure safety, efficacy, and quality (Choi, 2005).

Immunomodulators have been used to restore imbalances in the immune system in the body. Immunomodulators are natural, biological, or synthetic substances that can enhance, inhibit, or modulate the innate and adaptive functions of the immune system. Interest in immunomodulators is increasing due to greater awareness that many human diseases are associated with pathologically significant immune disorders and expanded knowledge of immune function (Saroj, 2012). Immunomodulation is the process of modifying the immune response by administering drugs or compounds, while immunomodulators are substances used to modulate components of the immune system. There are three stages of the SARS COV-2 virus infecting the human body stage I: asymptomatic incubation period with or without detectable virus, stage II: the period of mild symptoms in the presence of the virus, stage III: stage of severe respiratory symptoms with high viral load (Wang, 2020). Clinically, the immune response induced by SARS-CoV-2 infection is of two phases: during incubation and the non-severe stage, a specific adaptive immune response is required to eliminate the virus and prevent disease progression to a more severe location. Therefore, strategies to enhance the immune response (anti-sera or IFNα) at this stage are undoubtedly important (Shi, 2020). Genetic factors also have a role in maintaining the body's immune system (Asgari, 2021).

Several factors can cause the body's immunity down, such as irregular sleep patterns, stress, pollution, unhealthy eating patterns, lack of physical activity, and pollution. Therefore, we need a substance that can stimulate an increase in the body's immune system called an

immunomodulator (Gombart, 2020). Herbal plants classified as immunomodulators could encourage the immune system to fight diseases caused by infections, not work directly against microorganisms (Catanzaro, 2018). Some natural plants that have potential as immunomodulators are papaya leaves (Carica papaya L.), meniran (Phyllanthus niruri L.), Turmeric (Curcuma domesticae), Echinacea angustifolia, Andrographis paniculata, Allium sativum, and Zingiberis officinalis (Catanzaro, 2018; Otsuki, 2010; Gede, 2021; Yuandani, 2021; Rajanna, 2021; Ansary, 2020; Amri, 2016). The Brotowali plant (Tinospora crispa L) in Indonesia is known as "antawali" or "andawali" and is known to have properties to increase appetite and tonic (Koay, 2013).

Based on research conducted by (Otsuki, 2010), papaya leaf extract can inhibit the growth of tumor cells and various allergic disorders. The results showed that papaya leaves contain chemicals, such as -tocopherol, lycopene, flavonoids, and benzyl isothiocyanate, which can increase the production of Th1-type cytokines such as IL-12, IFN-γ, and TNF-α and Th-2 (Singh, 2020).

Tonic is a drug that strengthens the body and stimulates appetite. The tonic effect is an effect that promotes and enhances organ systems and encourages the repair of muscle tone cells. This tonic effect occurs because of the stimulatory effect on the central nervous system. This tonic effect can be classified as a psychostimulant. Psychostimulant compounds can increase the ability to concentrate the capacity concerned. Ginger (Zingiber officinale Rosc.) is a spice and medicinal plant that has long been known to the Indonesian people (Adnyana, 2017). Besides being used as a seasoning for cooking and traditional ingredients, this plant is also a trade commodity as an industrial ingredient for medicines, cosmetics, beverages, snacks, and kitchen necessities.

There are several chemical compounds in ginger, including essential oils such as n-nonyl aldehyde, d-camphene, d-β phellandrene, methyl heptenone, cineol, dborneol, geraniol, linalool, acetates and caprylate, citral, chavicol, and zingiberene. The characteristic properties of ginger are due to the presence of essential oils and ginger oleoresin. The fragrant aroma of ginger is caused by the essential oil, while the oleoresin causes a spicy taste. The compound that acts as a tonic or stimulant in the ginger extract is the oleoresin compound. So that ginger can be used as a tonic to cause a fresh effect and provide a stimulus (Mao, 2019).

III. Discussion

This perspective will be the pioneer to provide an overview of the herbal plants growing enormously in Indonesia regions which have immunomodulator and tonic properties to tackle the COVID-19 pandemic and become one of the solutions to society to maintain body health. Therefore, a safer and more effective drug is needed as an alternative. Natural products remain one of the essential new and secure sources for use as medicine for the human body.

The activity of a compound that can stimulate the immune system does not depend on the size of a particular molecule. This effect can be exerted by both small molecular weight compounds and by polymeric compounds. Therefore, efforts to search for such compounds can only be carried out using immunobiological test methods (Shi, 2020).

Methods of accelerating drug/vaccine approval by considering efficacy and safety need to be applied to help flatten the COVID-19 incidence curve in the world. We believe that natural products may play an important role and contribute to the development of antiviral drugs. Exploring antiviral medicinal plants as adjunctive or supportive therapy seems the right choice for managing this medical crisis. Natural ingredients can treat symptoms such as fever, cough, and boost immunity in COVID-19 patients. Detailed studies should be conducted on potential natural products alone or combined with antiviral therapies to

investigate their role in fighting COVID-19. Therefore, it will take time to work parallel on various strategies such as genetic engineering, in silico approaches, herbal remedies, and drug repositioning to achieve the common goal of finding a treatment for COVID-19 as early as possible.

3.1 Papaya Leaf (Carica papaya L)

Papaya leaf extract has the potential to inhibit the growth of tumor cells and various allergic disorders (Singh, 2020). The results showed that papaya leaves contain chemicals, such as alpha-tocopherol, lycopene, flavonoids, and benzyl isothiocyanate, which can increase the production of Th1-type cytokines such as IL-12, IFN-γ, and TNF-α and Th-2. Carica papaya has a rich source of three potent antioxidants, namely, vitamin C, vitamin A, and vitamin E; it also contains mineral ingredients, among others; magnesium and potassium; B vitamins include pantothenic acid and folic acid and are high in fiber (Wall, 2006; Ayoola, 2010; Somanah, 2017).

Figure 1. Papaya (*Carica papaya*)

3.2 Turmeric (Curcuma domestica L)

Turmeric have been familiar in society. It is originally cultivated in several region and popular in India, Southeast Asia including in Indonesia (Paramasiyam, 2009). Turmeric contains compounds that have medicinal properties, called curcuminoids, which consist of curcumin, desmethoxycurcumin and bisdemethoxycurcumin, and other beneficial substances: essential oil/Volatile oil (5.8%), sesquiterpene (53%), borneol (0.5%), cineol (60%), zingiberene (25%), sabinene (0.6%), fat 5.1%, carbohydrate 69.4%, protein 30%, starch/fat 8 %, vitamin C 45-55%, and mineral salts (iron, phosphorus, and calcium) (Amalraj, 2016). Turmeric has enormous pharmacological effects in human body such as anti-inflammatory, antioxidant, anti-fungal, anti-microbial, anti-malarial, anti-tumor, anti-aging (Changtam, 2010; Panahi, 2014; Kalpravidh, 2010; Khan, 2012; Zhan, 2011; Aditya NP, 2012; Peret, 2005).

Figure 2. *Turmeric (Curcuma domestica L)*

3.3 Meniran (Phyllantus niruri L)

Meniran has properties as an antiviral property. Immunomodulator compounds can improve the body's cellular and humoral immune systems (Sukmanadi, 2020). The content contained in meniran, namely flavonoid compounds as antioxidants that are stronger than vitamin E, these compounds can stimulate immunity. Meniran contains flavonoids that attach to immune cells and provide intracellular signals or stimuli to activate immune cells to work better. The application of flavonoids is extensive, namely, to treat bacterial infections and viral infections. Research shows that meniran functions to inhibit DNA polymerase from viruses inhibit reverse transcriptase enzymes from retroviruses, as antibacterial, antifungal, antidiarrheal, and other gastrointestinal diseases (Tjandrawinata, 2017). In addition to flavonoids, meniran also has filatin and hepofilatin, which are the main components that are efficacious in protecting the liver from toxic substances, both in the form of parasites, drugs, viruses, and bacteria (Hutomo, 2018). Liver cell repair is made possible by the content of active substances, namely filatin and hepofilatin, which activate Kupffer cells to produce interleukins for the regeneration of liver cells. According to the theory, Kupffer cells can produce interleukin 6, stimulating protein synthesis in liver cells (Ezzat, 2020). Therefore, meniran has an antihepatitic effect.

Figure 3. *Meniran (Phyllantus niruri L)*

3.4 Brotowali (Tinospora crispa L.)

The Tinospora crispa plant contains various chemical compounds, including alkaloids, soft resin, starch, glycosides, picroretosides, harsa, and bitter substances picroretin and tinocrisposide berberine, palmatine, columbin, and kaolin or picrotoxins. Tinospora crispa has been widely used for medicine. Crude extract from Tinospora crispa can be used as an anti-inflammatory, anti-diabetic, antimalarial, and analgesic (Ahmad, 2016). In general, brotowali contains chemical compounds such as columbin, palmatine, tinocrisposide, picroretin, picroretoside, soft resin, bitter substances, starch, alkaloids, glycosides, harsa, berberine, and picrotoxins or kaokulin. Based on the compounds contained in the brotowali plant, several pharmacological effects can be used to cure various diseases. Brotowali can provide pharmacological effects such as antiperiodic, tonic, anticoagulant, analgesic, anti-inflammatory, and diuretic (Ahmad, 2016).

Many food and plant substances known to exhibit antiviral and immunomodulatory activity such as Aloe vera, Angelica gigas (Korean angelica), Astragalus membranaceus (Mongolian milkvetch), Ganoderma lucidum (lingzhi mushroom), Panax ginseng (ginseng), and Scutellaria baicalensis (Chinese skullcap) have been studied and reported to exhibit immunomodulatory properties (Tan, 2004).

Figure 4. *Brotowali (Tinospora crispa)*

3.5 Ginger (Zingiber officinale Rosc.)

Red ginger is more widely used as a medicine because it contains the highest essential oil and oleoresin, so that it is more effective in curing various types of diseases. The red ginger important oil content ranges from 2.58-3.72% (Kurniasari, 2008). In addition, the oleoresin content of red ginger is also higher than other gingers, which is 3% of dry weight (Kurniasari, 2008). The compound that is thought to act as a tonic or stimulant in ginger extract is oleoresin compound (Koga, 2016). Ginger oleoresin is a thick yellow liquid with a sharp spicy taste, soluble in alcohol and petroleum ether, and slightly soluble in water (Mahboubi, 2019).

Figure 5. *Ginger (Zingiber officinale Rosc.)*

IV. Conclusion

This paper has suggested that with Indonesia's rich natural resources, several natural plants that have potential as immunomodulators are papaya leaf (Carica papaya L.), Meniran (Phyllanthus niruri L.), Turmeric (Curcuma domesticae), Echinacea angustifolia, Andrographis paniculata, Allium sativum, and Zingiberis officinalis. The Brotowali plant (Tinospora crispa L) is known to have the property of increasing appetite and tonic. The four preparations above should be continued in research to produce herbal preparations for handling COVID-19.

Furthermore, this paper has suggested that this crisis of using herbal medicine in some diseases, such as this moment in the COVID-19 pandemic, had few opportunities to explore the nation's resources to create sovereignty of producing substances to healing. Collectively, the use of immunomodulatory herbal medicines is thought to have an activity to increase the immune system and protect the body against COVID-19. However, these observations should be verified through further scientific studies or clinical trials. For further, further research can be carried out.

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