Indonesia's Potential for Elucidating New Therapeutic Treatments for COVID-19

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Abstract

Many therapeutic strategies have been devised to combat the COVID-19 pandemic, including the development of new vaccines, the administration of antivirals, and the use of plant-derived medicines. Unfortunately, the current strategies are either not yet available, or have not convincingly and unequivocally shown the desired efficacy needed to combat the pandemic. The identification of active compounds in plant-derived medicines can lead to new antivirals in the future, which makes plant biodiversity an indispensable resource. Countries that have high biodiversity such as Indonesia can play an important role in the elucidation and development of new plant-derived medicines and antivirals. In this article, we highlight the potential of Indonesia's assets such as its plant diversity and a strong history of utilizing traditional medicines to fight the current pandemic. We also introduce possible roadmaps for the development of new treatments from the assets and policy interventions that can be implemented.

1. Introduction

The COVID-19 pandemic has wreaked havoc on many aspects of life. So much so to the point where national and global agendas have been halted and reconsidered (van Staden, 2020). The pandemic has caused the slowing down of the global economy (Gopalan & Misra, 2020; Nicola et al., 2020), reorientation of education systems (Teräs et al., 2020), revamping of healthcare systems (Miller et al., 2020; Ming et al., 2020), mass environmental changes (Lal et al., 2020; Shakil et al., 2020; Somani et al., 2020), to even the halt and reorganization of professional sports (Corsini et al., 2020; Difiori et al., 2020).

Indonesia is one of the countries that has been hit hard by the current pandemic in many aspects (Setiati & Azwar, 2020). The Indonesian Government has implemented many strategies to balance the welfare and the wellbeing of its citizens, including the implementation of large scale social restrictions, which have proven to be not as effective as desired (Purnama & Susanna, 2020; Suraya et al., 2020).

The large scale social restrictions were meant to keep the economy running, while protecting citizens from new infections, because if left uncontained, there is a large possibility of the occurrence of a large scale outbreak (Aldila et al., 2020). In fact, at the time of this writing, the infection rate in Indonesia has gone up to approximately 5,000 infections per day, with a rising trajectory (Komite Penanganan COVID-19 dan Pemulihan Ekonomi Nasional, 2020). The increasing number of infections will inevitably have negative implications on the economy, which is exactly what the Indonesian Government is trying to avoid.

A lot of hope is being put on new vaccines to turn the tide and reduce the number of infections and return to pre-pandemic normalcy. However, successful implementation of vaccinations to slow down the pandemic depends on several factors, including the effectiveness the vaccines, the prices in which they are available, and how widespread the vaccinations can be implemented at a certain time period (Harapan et al., 2020). In addition, for the time being, there are still some *caveats* or risks that are related to the implementation of vaccines, which we will further elaborate (W. H. Chen et al., 2020).

Another option, which also has potential in fighting the pandemic and other novel diseases, is by using plant-derived medicines (Ghildiyal et al., 2020; Weng, 2020; Wink, 2020). Indonesia can play a significant role in the effort of elucidating novel treatments from plants. Mainly due to its immense biodiversity (Ragamustari & Sukara, 2019) and its strong and long tradition in using plant-based medicines (Elfahmi et al., 2014; Hartono Wijaya et al., 2016; Stevensen, 1999).

Unfortunately, there are also bottlenecks and challenges in the development of new plant-based medicines in Indonesia that need to be managed, from the low science and technology capacity, underdeveloped national innovation system (Ragamustari et al., 2020), to the mismanagement of natural resources (Ragamustari & Sukara, 2019). The roadmap to develop new plant-based medicines, especially to fight the current pandemic (from an Indonesian perspective) is the main topic of the current article.

2. The challenges for developing a new vaccine for COVID-19

There are important considerations for mass application of a vaccine for COVID-19, namely its effectiveness and safety. The vaccine needs to show high efficacy, while at the same time be safe for the vaccinees. Finding a silver bullet will be problematic because people who are infected might show different physiological reactions toward a certain vaccine. Thus, some safety measures related to the choice of vaccine platform, choice of adjuvant, mode/route of vaccine administration, age of vaccinees, and pre-existing immunity need to be meticulously considered (Jeyanathan et al., 2020).

The attempt in developing a new vaccine for COVID-19 immediately began after the outbreak in its origin place at Wuhan, China at the end of 2019. By January 2020, the genetic sequence of the SARS-CoV-2 virus, which causes the COVID-19 disease was published (Thanh Le et al., 2020). The genetic sequence became a basis for laboratories and vaccine manufacturers to produce a vaccine for COVID-19. As of July 2020, there are already more than 160 vaccine candidates that have been developed by various laboratories and companies. However only a small amount have entered into I, II, and III clinical

trials (Jeyanathan et al., 2020).

Generally, there are six categories of technologies or approaches that are used to develop a vaccine for COVID-19, which include: 1) live attenuated virus, 2) recombinant viral-vectored vaccines, 3) inactivated or killed viruses, 4) protein subunit vaccines, 5) virus-like particles, and 6) nucleic acid based (mRNA and DNA) vaccines. Each of the technologies have pluses and minuses. Out of the six categories, the total number of vaccines per July 2020 that have gone into pre-clinical trial is 139, while the number of vaccines that have gone into clinical trial is 27. None from the live attenuated virus category have gone into clinical trials, while at least one of vaccine from the other categories have gone into clinical trial. The three best COVID-19 candidates are viral vectored and mRNA-based vaccines (W. H. Chen et al., 2020; Jeyanathan et al., 2020).

There several underlying reasons for the slow progress of the development of a working and effective vaccine for COVID-19. One of them is the highly mutative nature of the SARS-CoV-2 virus (Lal et al., 2020). In addition, the mechanisms of COVID-19 infection and immune responses are not yet well understood (Jeyanathan et al., 2020). In fact, there are cases in which the SARS coronavirus vaccines may actually result in increased infectivity, which is dangerous for the person who is infected (W. H. Chen et al., 2020).

Another factor that will affect the timeline of mass application of a vaccine (if a working and effective one is developed) is a strategy for mass vaccination, which is related to production capacity of the vaccines. Ideally, the scenario will consist of three stages. The first stage is when there is limited supply of the vaccine. The vaccinees to be prioritized will be those who have the highest risk of mortality, such as people who have co-morbidities, health workers, the elderly, and ethnic minorities who have been hit the hardest by the pandemic. The second stage will be focused on individuals who were already infected but have recovered, were vaccinated during the medical trials (with candidate vaccines), or people who have been vaccinated in the first stage but have not developed adequate immunity to the virus. All of these groups have similarity in that all have waning immunity and are susceptible to future infections. The last stage is the period when there is enough vaccine supplies to conduct mass vaccinations, where vaccinations will be carried out and coordinated at the national level for the masses (Jeyanathan et al., 2020). In normal conditions, rationally, the mentioned scenario might take 10-15 years. But due to the urgency of combating the pandemic, it is compressed into 1-2 years.

Despite the laborious efforts to develop a vaccine for COVID-19, there is no guarantee that a working vaccine will be available anytime soon. Thus, it is imperative that alternative strategies to complement the effort to develop new vaccines for combating COVID-19 be done simultaneously. One strategy that has a potentially positive outcome is the use and development of antivirals.

3. The utilization of antivirals for COVID-19 treatment

Because of the unavailability of any working vaccines for the SARS-CoV-2 virus, the fight against the pandemic is still dependent on antiviral drugs and other methods. The antivirals being used for treatment of COVID-19 are ones that are used to treat other diseases caused by other viruses/organisms such as HIV, malaria, SARS-CoV, MERS, and influenza viruses (Jomah et al., 2020; Şimşek Yavuz & Ünal, 2020). Unfortunately, the efficacy of such

antivirals toward COVID-19 showed mixed results and are correlated with many factors that are yet to be elucidated (Jomah et al., 2020).

Understanding the types of antivirals available will help in devising a strategy that is best suited for combating COVID-19. Antivirals are generally divided into six categories, which include protease inhibitors, broad spectrum antivirals, RNA-dependent RNA polymerase inhibitors, nucleoside inhibitors, neuroamidase inhibitors, and polymerase acidic endonuclease inhibitors (Teoh et al., 2020).

One of the most popular antivirals that is used to treat COVID-19 patients is hydroxychloroquine (Vinetz, 2020). It originally wasn't an antiviral at all and was used for the treatment of malaria and autoimmune diseases. The drug inhibits certain cellular functions and molecular pathways (Şimşek Yavuz & Ünal, 2020), which in turn interferes with the entry of the SARS-CoV-2 into the host cell (Fredi-ansyah et al., 2020).

Early studies on efficacy of hydroxychloroquine toward COVID-19 reported that the drug showed antiviral activity toward SARS-CoV-2 and can be used for treatment of COVID-19 patients (Z. Chen et al., 2020; Gautret et al., 2020). These results have been the base for the authorization of the drug in national healthcare systems for treating COVID-19 patients. In fact, in Indonesia, the formal protocol for treating COVID-19 patients in the early stage of infection involve the administration of hydroxychloroquine along with azithromycin, vitamin C, and symptomatic treatments (Siswanto et al., 2020).

In reality, the administration of hydroxychloroquine for COVID-19 patients has shown mixed results. The very same report that showed hydroxychloroquine sped up the recovery time for some COVID-19 patients, also showed that the drug showed negative or no significant effect toward other patients. In addition, the report was also based on an imperfect research design that used a very small sample size and lacked important data such as the patients' cardiogram, total virus count and no placebo control (Z. Chen et al., 2020; Vinetz, 2020). However, it should be noted that placebo control is deemed unethical in the current pandemic situation. A more recent report on the administration of hydroxychloroquine have actually showed a range of different effects from no significant efficacy to the worsening of the condition of patients. In fact, it is not recommended for patients who experience pneumonia and require oxygen (Mahévas et al., 2020).

As mentioned earlier, Indonesia has been a strong advocator of the use of hydroxychloroquine and is still continuing to use it despite the antiviral being banned by WHO (Lamb & Allard, 2020). The reasons of the Indonesian Government's stance are due to the inconclusive results of clinical trials (on the efficacy or danger of hydroxychloroquine and other antivirals), the possible differences of Indonesian SARS-CoV-2 line with the one in other places (where there is still an open possibility that the antiviral have efficacy toward the Indonesian SARS-CoV-2 line), the differences in genetics of Indonesians with other populations (where there is a possibility that the physiology of Indonesians are suitable for the administration of hydroxychloroquine), and mainly, because of the lack of other options (Surbakti, 2020).

Besides hydroxychloroquine, there are other antivirals that have been authorized for COVID-19 treatment with varying degrees of success. For example, antivirals such as umifenovir, lopanovir, darunavir, atazanavir, saquinavir, emtricitabine, azvudine, remdisivir, favipiravir (Avigan), ribavirin, sofosbuvir, oseltamivit (Tamiflu) have all been

authorized for use in one country or another for emergency COVID-19 cases (Frediansyah et al., 2020). Remdesivir and lopinavir have specifically been authorized by the United States Food and Drug administration for treatment of COVID-19 in emergency cases that involve severe infections of adults and children in the US (Jomah et al., 2020).

It should also be noted that the administration of antivirals that were mentioned have risks such as adverse side effects and contraindications. Adverse side effects include a combination of one or more of the following: gastrointestinal effects, allergic reactions, hyperuricemia, diarrhea, decreased appetite, kidney injury, hyperglycemia, fever, fatigue, nausea, cardiac conduct abnormalities, pancreatitis, bronchitis, sinusitis, or other adverse effects depending on the antiviral drug being administered. Some of the drugs should also not to be used by certain groups of people, such as people with hypersensitivity, children under a certain age, and people who are pregnant (Teoh et al., 2020).

Although the administration of antivirals for COVID-19 patients, including the ones authorized for use by certain countries during emergencies have been a hit and miss, and there is not enough information to devise a clinical practice (Teoh et al., 2020), research on antivirals need to be continued. As it opens up the possibility of new therapeutic strategies by targeting specific stages of the SARS-CoV-2 life cycle (Frediansyah et al., 2020). Nevertheless, we are still in dire need for other therapeutic strategies for effectively combating COVID-19.

4. Plant-derived traditional medicines and treatment

The non-existence of a working vaccine and the erratic results of available antivirals have forced medical practitioners to look for alternative strategies to treat COVID-19 patients. One strategy that has been used and achieved a certain degree of success is the use of plant-derived traditional medicines (Yang et al., 2020).

Plant-derived medicines have been an integral part of human civilization since its beginnings (Weng, 2020). They are widely used all around the world and are intertwined with many traditional cultures, including China (traditional Chinese medicine), Japan (kampo), Indonesia (jamu), and India (ayurvedic medicine). In Europe and the United States, plant-derived traditional medicines have found their way through homeopathy and phytotherapy (Itokawa et al., 2008). Plant-derived medicines also still play an important role modern medicine, where approximately 25% of all the modern medicines are directly or indirectly derived from plants (Calixto, 2000). In addition, the majority of population in some countries, especially developing countries, still depend on plant-derived traditional medicines as their primary source of healthcare, mainly due to the limited access toward conventional health services (World Health Organization (WHO), 2013).

Two major characteristics of plant-derived traditional medicines and other phytoterapeutic medicines are as follows: 1) that the active principles and mechanisms that lead to their efficacy are generally unknown; and 2) the pharmacological action is usually not as strong as conventional medicines and does not show immediate effect (Calixto, 2000).

In comparison with the administration of vaccines or antivirals, plant-derived traditional medicines have several advantages. Among them is their availability and price. Especially if the ingredients for the medicine mixture is embedded in the

population's culture and history. In addition, plant-derived traditional medicines are generally regarded as relatively safe and shows less frequent adverse side effects if consumed within reasonable amounts (Calixto, 2000; Zeng & Jiang, 2010). However, it is worth noting that irresponsible administration of plant-derived traditional medicines has the potential to cause adverse side effects, especially for people who are simultaneously taking different medications, where it can trigger adverse drug reactions (Zeng & Jiang, 2010). Other risks that are related to the administration of plant-derived traditional medicines include poor quality products used in medication, unqualified practitioners, improper diagnosis, and misleading information from practitioners (World Health Organization (WHO), 2013).

In relation to the COVID-19 pandemic, several cases in China where plant-derived traditional medicines were used to treat COVID-19 patients have shown positive results (Weng, 2020; Yang et al., 2020). China is known to have a long history spanning over millennia of using plants in the form of Traditional Chinese Medicines (TCM) (Weng, 2020). TCM is also integrated into the Chinese healthcare system, which is coordinated by the National Administration of Traditional Chinese Medicine (NATCM), so administration of TCM is officially authorized for treating COVID-19 patients (Yang et al., 2020).

An example of a TCM showing efficacy that is being administered to COVID-19 patients in China is the lung cleansing and detoxifying decoction (LCDD) (Weng, 2020). LCDD was made based on a classical literature wrote by Zhang Zhonjing (AD 150~219), titled *Treatise on Cold Pathogenic and Miscellaneous Diseases.* Four classical formulas were used as the basis to make LCDD, which contains 21 different plant species. After the authorization of its use, LCDD has been widely used in China by 28 provinces and municipalities (Weng, 2020).

Thus, it is indeed possible to develop new plant-derived medicines based on traditional knowledge. However, the process might not be as straightforward as it is in China. There are many bottlenecks in the adaptation of traditional medicines such as LCDD outside of China. These bottlenecks include 1) the lack of societal and cultural acceptance and trust toward traditional medicines, 2) the lack of institutional structure to support the transition of traditional medicines for use in conventional healthcare system, and 3) the lack of understanding of the science behind traditional medicines result in low acceptance by patients and physicians (Weng, 2020).

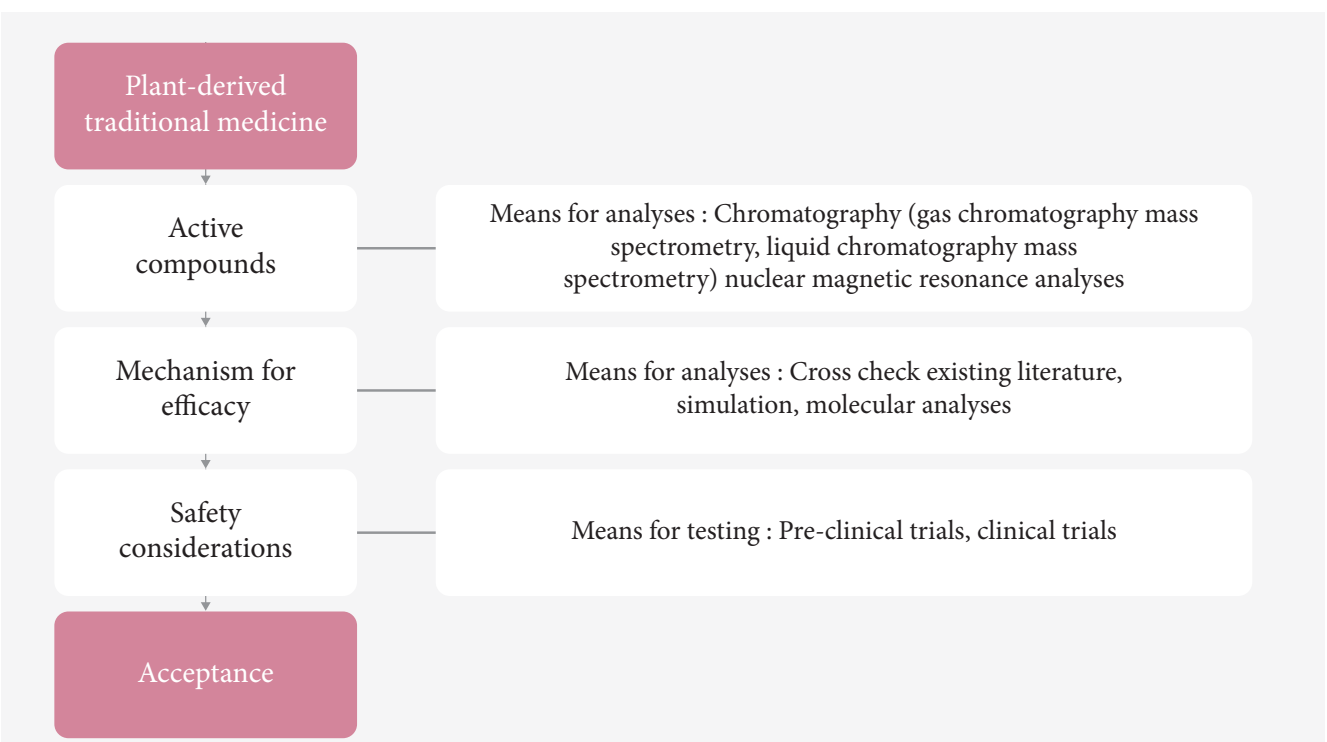
The first bottleneck can be managed by education and propaganda by the government of a nation. This bottleneck will differ depending on a country's social and cultural makeup. Indonesia for example, has a long and strong history in using traditional medicines, which make this bottleneck less significant. The second bottleneck can be managed by designing new institutions and policies that support the transition of traditional medicines into the conventional healthcare system, akin to China's NATCM and TCM adaption roadmap. Indonesia actually has a national commission for the scientification of jamu, which was formed in 2013 through the decree of the Indonesian Ministry of Health Number 296/MENKES/SK/VIII/2013. Unfortunately, there is very little information on what the commission has been doing since its inception. The last bottleneck can be managed by providing better scientific evidence on the mechanisms of the efficacy of plant-derived traditional medicines. There are already many researches that have been done on the subject (Kartini et al., 2019; Sumarni et al., 2019), but need to be compiled into a structured database.

5. The science behind plant-derived traditional medicines

As has been mentioned, understanding the science behind plant-derived traditional medicines is an important step for acceptance by patients and physicians so that their transition into conventional healthcare systems can take place.

Generally, plants exhibit therapeutic attributes because of secondary metabolites they produce. In relation to the current pandemic, secondary metabolite groups that exhibit antiviral activity that have the potential to be used against SARS-CoV-2 include phenolics, terpenoids, and alkaloids. The largest group of plant secondary metabolites that show antiviral activity is phenolics, which consists of phenolic acids, flavonoids, stilbenes, coumarins, and tannins (Itokawa et al., 2008; Jahan & Onay, 2020). Thus, the first step to establish the scientific foundation of plant-derived traditional medicines is by elucidating the bioactive compounds they produce as secondary metabolites.

Once secondary metabolites from the plant-derived medicine have been purified and identified, the mechanisms of their therapeutical attributes need to be elucidated. There are two ways to do this. First, we can refer to past researches that have elucidated the therapeutical mechanisms of the identified compounds, which are generally elucidated through molecular analysis (Dao et al., 2012; Lin et al., 2005). If there is not yet any information on the compound's therapeutic mechanisms, molecular analyses needs to be conducted. After establishing the types of compounds and the mechanisms of their



[Figure 1] *Scientificiation* process of plant-derived traditional medicine

therapeutical attributes, the scientific groundings can be further strengthened by conducting pre-clinical and clinical trials of the plant-derived medicine. A graphical representation of the whole scientification process can be seen in Figure 1.

It is important to note that each of these steps require a lot of investments in the form of infrastructures, especially those that are related to tools for analyses, such as PCR thermocycles, chromatography equipment, nuclear magnetic resonance equipment, etc. (Figure 1). Ideally the funding for equipment should be burdened on the government because it is related to the national interest.

6. Indonesia's plant-derived traditional medicine and plant diversity

The scheme that was provided for the *scientification* process of plant-derived traditional medicines can be used by Indonesia to optimize two of its main assets for fighting the pandemic. The assets include immense traditional knowledge on plant-derived medicines and immense plant diversity to support it.

Indonesian plant-derived traditional medicine or *jamu*, is in many ways similar to that of TCM in China. Both are embedded in the culture of the societies and are still used for the treatment of many kinds of sickness (Elfahmi et al., 2014; Weng, 2020). However, the way the Indonesian Government treat *jamu* is different from how the Chinese Government is treating TCM, at least in the way both heritages are positioned in their respective healthcare systems. Whilst TCM is being incorporated in the Chinese healthcare system and is being used officially for the treatment of COVID-19, *jamu* is still in a different category from conventional medicines. Plant-derived traditional medicines are further divided into three categories that include herbal medicines, scientific-based herbal medicines, and clinical-based herbal medicines, with the majority of *jamu* being in the first (lowest) category with no scientific grounding whatsoever (Tripoli & Wahyono, 2015). Ideally, all *jamu* should be moved to the third category (clinical-based herbal medicines), which has the highest legitimacy to be used for treatment of sickness.

In the context of the current pandemic, more focus should be put on *jamu* mixtures that have highest probability as treatment for COVID-19. The measurement of the probability can be done by rationalization and comparing certain *jamu* with TCM that have successfully been used for treating COVID-19 (Hartanti et al., 2020). The *jamu* that have been screened can then be put into the pipeline for *scientification* that was previously mentioned. However, in addition to pushing *jamu* as an alternative treatment there also needs to be adequate information to the public of the danger of unauthorized traditional medicine (*jamu*) for COVID-19 treatment (Lim & Pranata, 2020).

In addition to the immense knowledge on *jamu* that can be a starting point for the elucidation of novel COVID-19 treatments, Indonesia also has immense potential in the form of its biodiversity (Mittermeier et al., 1997), specifically its plant diversity. Indonesia is the home of 80% of all medicinal plants in the world and has 1,845 forest plant species that can readily be used for medicines (Elfahmi et al., 2014).

There have been other researches and projects dedicated to discover and identify Indonesian plant diversity. One of the most notable is the project done by Plant Resources of South East Asia (PROSEA), which was done from 1985 to 2016 by the PROSEA Foundation (*PROSEA Plant Resources of South East*

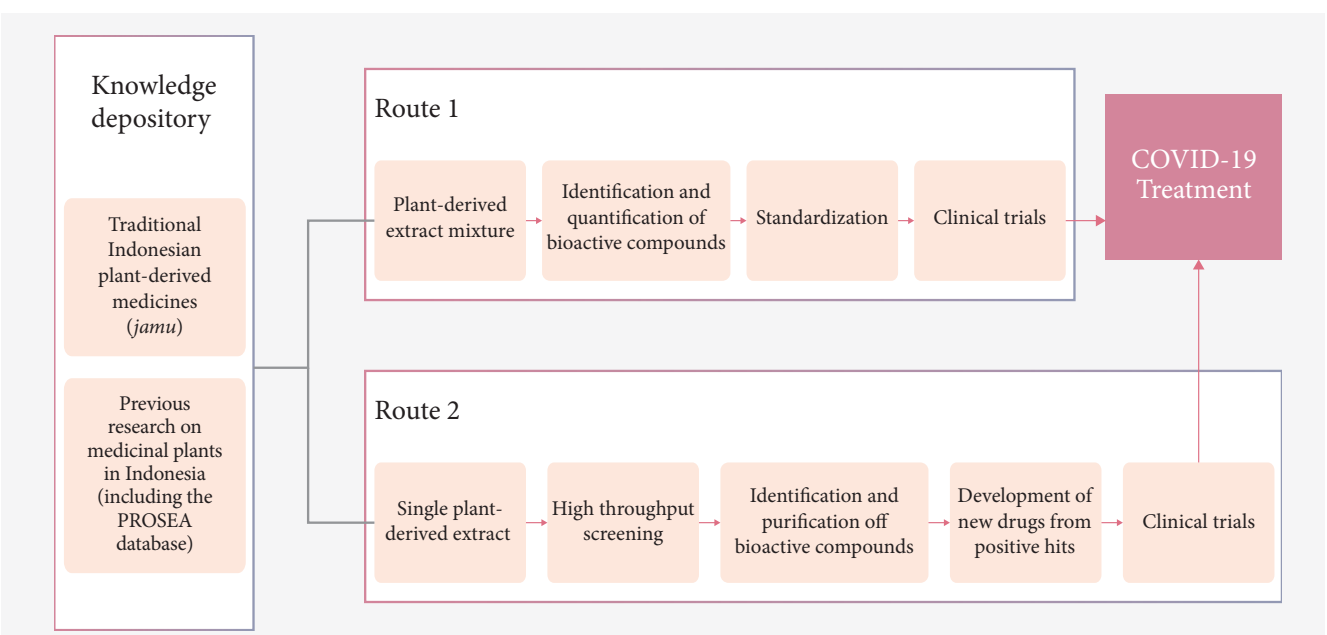
Asia Website, 2020). The project was an international collaboration and produced 19 book volumes containing a database of plants in different categories. Three volumes were dedicated to medicinal and poisonous plants, where 1,141 species were identified and characterized (de Padua et al., 1999; Lemmens & Bunyapraphatsara, 2003; van Valkenburg & Bunyapraphatsara, 2002). In addition to the PROSEA project, there have been research that follow it up and discovered there were actually more species, which weren't covered by the PROSEA books (Roosita et al., 2008; Van Sam et al., 2008), opening up even more possibilities.

The information from such researches and projects can be a starting point for the screening of plants that have antiviral attributes. A high throughput screening method such as the ones done in previous researches (Min et al., 2018; N. Powers & N. Setzer, 2016) could quickly help determine preliminary candidates that can be further be assessed for their antiviral activities, especially toward COVID-19.

7. A putative roadmap for the development of new treatment strategies for COVID-19 in Indonesia

From the above, we can design a putative roadmap for the development of novel treatment strategies for COVID-19 (Figure 2). In the roadmap we have made, there are two pathways in developing novel treatment strategies, which are by 1) using whole extracts of medicinal plant mixtures based on rationalization of *jamu* or 2) using high-throughput screening of plants that potentially have antiviral secondary metabolites.

The first pathway is similar to what has been done in China with TCM-based treatment for COVID-19, which might offer synergistic effects of many different plant metabolites against SARS-CoV-2.



[**Figure 2**] A putative roadmap for the development of novel treatment strategies for COVID-19

The most important aspect is the standardization of the amounts of each ingredient in the medicine mixture to avoid adverse effects. The second pathway is the bioprospecting the exact compounds that are responsible for the efficacy toward the virus.

In both pathways, knowing the metabolite contents of the mixtures or plants is essential. This process will need analyses tools such as chromatography apparatuses to detect, identify, and purify the metabolites. To take it even further, metabolite pathways and gene networks can be established to set up systems for producing target metabolites with the help of synthetic biology. Chromatography apparatuses such as High-Performance Liquid Chromatography, Gas Chromatography Mass Spectrometry, and Liquid Chromatography Mass Spectrometry will be essential for this step. Other analysis apparatus for detailed identification of the metabolites such as Nuclear Magnetic Resonance spectroscopy will also be indispensable. In addition, kits and apparatuses that are important for molecular analysis will also be indispensable.

It is worth noting that the price of such apparatuses can be quite expensive, reaching up to 200,000 USD per apparatus. Not to mention the day-to-day operation and analyses costs that need to be continuously be provided. Thus, in the context of Indonesia, where such apparatuses are either not available or not readily accessible, their procurement or re-inventory needs to be done, preferably by the Indonesian Government.

The Indonesian Government has made a committee for combating COVID-19 and restoration of the national economy (*Committee for COVID-19 and National Economy Restoration Website (Komite Penanganan COVID-19 Dan Pemulihan Ekonomi Nasional*), 2020). However, there is no clear definition or information on what the committee is responsible for and its job description. For the realization of the roadmap that we have shown, there needs to be an *ad hoc* committee in charge of it, and is preferably directly under the highest authority, which in the case of Indonesia, is the President. The committee also needs to be given the freedom to connect important stakeholders and conduct activities that can support the realization of the roadmap.

8. Science and technology capacity are key to unlocking the potentials of biodiversity

The mastery of science and technology (S&T) is one of the key aspects in being able to unlock the potentials of natural resources and convert them into products with higher value (Ragamustari & Sukara, 2019). The success of the roadmap that we introduced is also very much connected, if not dependent on Indonesia's S&T capacity.

One concept that is often used to understand the state of a country's S&T capacity is the National Innovation System (NIS) (Lundvall, 2007; Lundvall et al., 2002). This concept is then interpreted in many ways to analyze S&T and innovation capacity of a country using multidisciplinary approaches. For example, a previous research introduced the National Innovation Capacity concept that was derived from NIS, and was used to rank the innovation capacities of different countries (Rongping et al., 2019). In another research, the NIS was used to identify the evolutionary dynamics of S&T capacity of different countries (Ragamustari et al., 2020).

The similarities between researches based on NIS is the agreement that one of the most important aspects of a nation's S&T and innovation capacity

is the commitment toward S&T, which is indicated first and foremost by the amount of expenditure for research and development of new technology. In this aspect, Indonesia needs much improvement, as its gross expenditure on R&D is only 0.2% of its GDP (latest available data, 2018), which is low even in comparison to its regional neighbors such as Malaysia (1.44%, 2016), Thailand (1%, 2017), or even Vietnam (0.53%, 2017), let alone developed countries (UNESCO, 2020). This needs to change, because research is not cheap, and as mentioned earlier, the procurement and maintenance of the tools needed for continuous research related to the roadmap for the COVID-19 treatment development can be very costly.

Besides the amount of expenditure being put into the research and development pipeline, other basic indicators for science and technology capacity include number of researchers, institutions for S&T capacity development, number of patent applications, number of scientific articles produced, and revenue from high-tech products, all in which Indonesia is lacking except for the number of institutions for S&T development. In addition, Indonesia also still suffers from a lack of identity on how its S&T is developing (Ragamustari et al., 2020).

There are several things that can be done to improve Indonesia's current S&T capacity, which include: 1) the reformation of institutions involved in S&T capacity development (including how they interact among each other and with other important stakeholders), 2) Increase GERD as percentage of GDP to a certain target, 3) incorporate industry in the development of S&T capacity, and 4) make a large scale propaganda on the importance of S&T capacity (Ragamustari et al., 2020).

The process of increasing Indonesia's S&T capacity is long-term, and for combating the current pandemic, the country needs to more pragmatic and work with what it currently has. Nevertheless, if Indonesia can reach a certain threshold of S&T capacity, and a clear direction to it (preferably one that is geared toward utilization of its biodiversity), Indonesia can no doubt produce many important products that are needed globally. In relation with COVID-19, an adequate level of S&T capacity will help Indonesia realize the roadmap that was introduced efficiently and optimally.

With the era of synthetic biology dawning upon us (Awan et al., 2016; Guzmán-Trampe et al., 2017; Lee et al., 2012), Indonesia's biodiversity is of immense potential. Perhaps in the future, as mentioned earlier, novel antivirals can be produced through synthetic biology, based on plant metabolites that are found from Indonesian biodiversity.

9. Conclusion

Without a working vaccine, erratic results of administration of available antivirals, and the difficulties of introducing plant-derived traditional medicines to conventional healthcare systems, all possible strategies to combat the COVID-19 pandemic need to be done.

For Indonesia, a country with immense biodiversity and strong history in the use of plant-derived traditional medicines, devising strategies to combat the pandemic based on those two assets make a lot of sense. From those assets, new treatments and products to combat COVID-19 can be developed, granted that there is a clear roadmap for development, adequate supporting system/bureaucracy, and S&T

capacity. Indonesia's success in developing new treatments and products will also benefit the global community.

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