

Preventive Medicine of Covid-19 Traditional Local Knowledge In Indonesia and Malaysia

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BIORESOURCES UTILIZATION FOR COVID-19 STUDIES: USAGE OF *SACCHAROMYCES CEREVISIAE* AND NONI (*MORINDA CITRIFOLIA*) FRUIT IN A RESEARCH

**Hermansyah Hermansyah, Dwita Oktiarni, Getari Kasmiarti, and
Susilawati Susilawati**

Bioresources are the sources biodiversity that have potential to be utilized as food, energy, pharmaceutical, material, environmental services, and other industries. The first benefit that can be taken from bioresources is as a source of food, carbohydrate foods such as root crops or colorful vegetables and fruits. Advanced technology helps the herb medicines with the to development of every nutritious part of the plant as many ailments' curer. In addition, the abundant bioresources can be managed smartly and wisely by producing various products in cosmetics and herbal medicinal industry. The most important benefit of biodiversity is to balance the ecosystem. Every living thing that inhabits an ecosystem has its role. If the existence of these living things is threatened, it will certainly disturb the balance of the ecosystem.

The sustainable use of bioresources is carried out by cultivating system. Bioresources can be grown and harvested at certain times based on the utilization pattern. Moreover, this system provides any information related to bioresources controlling and monitoring for future development. Nowadays, many plants become the center of attention in helping to develop good health. The open access of bioresources makes an easy way for the researcher to discover the active substances which play a role in treating diseases. This paper highlights *Morinda citrifolia* (*M. citrifolia*) as the focus of further explanation.

M. citrifolia is widely known as 'noni' which is found in Southeast Asia, Hawaii and Polynesia (Cruz-Sanchez et al, 2019; Almeida et al, 2019). In Malaysia and Indonesia, *M. citrifolia* is called as *Mengkudu* (Figure 1.6). People usually make use of this as traditional medicine and food (Assi et al, 2017; Shalan et al, 2016). Noni plants classified as **perennial** plants with unique morphology with a small trunk, broadleaf, and the other part are **roots, stems, leaves, fruit and seeds**. A taproot constructs **the root** itself through **the** deep soil together with the fine roots. **The trunk (caulis) and branches (ramus) are elliptical, generally bent, rough-skinned, and dark brown. Naturally, the plant height can reach about 6-8 meters. The leaves**

5
(folium) of the noni plant grow in pairs on each branch. The leaves are dark green, hairless, and oval in shape with pinnate leaf veins. The flowers (flos) of the noni plant are small, grow between two leaves, and are tightly packed together, and are arranged in bunches (compound flowers). The compound flowers will turn into fruit, which is round or elliptical with the tip getting smaller and blunt, lumpy, and somehow like a pineapple. It has three different colors which are green (young), yellow or white (mature), and brownish-smelly when it's ripped with soft texture. The seeds could be described as oval and small-sized, dense, and blackish brown. Generally, the fruits, leaves, seeds, and roots can be processed into useful products especially in the healing treatment. Due to the many advantages of *M. citrifolia*, many investigations have been conducted to study about the bioactive materials in it, including the mechanism (Inada et al, 2017).

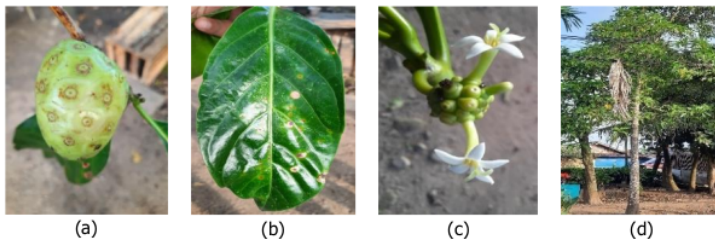


Figure 1.6: *Morinda citrifolia* or Noni plant (a) fruit, (b) leaf, (c) flower, and (d) tree
(Photograph by Hermansyah Hermansyah)

The bioactive substances in *M. citrifolia* highly respond into immunomodulatory, anti-inflammation and antioxidant changing (Liu et al, 2018; Lohani et al, 2019; Torres et al, 2017). Chemical compounds were discovered like iridoids, anthraquinones, flavonoids, and others (Almeida-Souza et al, 2018; Inada et al, 2020; Li et al, 2020). The seeds contain a high number of fiber and free radical scavenging. Furthermore, the pulp is composed of phenolic compounds and the skin consists of antioxidant content (Nascimento et al, 2018). The leaves extracted traditionally by Polynesia indigenous as anti-inflammation, skin injuries, and fatigue recovery (Wu et al, 2015). In addition, Souse et al. (2017) claimed that noni consumption did not show side effects in liver or kidney excluding the immune system. Noni could become the pilot plan in discovering new treatment related to oxidative stress for chronic and dietary cases

(Sina et al, 2021). Even though noni plant can improve human health as a result of advanced medicine, the mechanism itself remains unknown in certain conditions (Hong et al, 2019). Corona virus outbreak emerged in Wuhan, China at the end of 2019. The occurrence of rapid transmission cases and the absence of an anti-virus have caused it to become a global pandemic. Many scientists are trying to report a solution to combat this pandemic including proposing herbal medicine as the way out. In Makassar (South Sulawesi) Indonesia, claims have been made that 33 COVID-19 patients recovered after consuming noni juice, as reported by the Times Indonesia news (Friday, 22/5/2020). Noni juice was given to 33 patients who were tested positive for the corona virus and undergoing treatment at Dadi Hospital in Makassar. Based on this case, there must be strong correlation between noni plant and corona virus because noni plant itself was used as a therapeutic remedy to various diseases as an antibacterial, antitumor, anthelmintic, analgesic, anti-inflammatory, immunostimulant with its bioactive abilities. It also proved that noni plants are beneficial for respiratory infections (Ali et al, 2016). The immune system has evolved to protect us from infection of pathogens including virus. Noni plant especially the fruit may improve our body's immune system as when used in many people when their body is infected. While phytochemicals analysis indicates that Noni fruit juices with or without seeds regulate cell-mediated immunity and antioxidant enzyme based on immunity performance (age restricted) (Pratap et al, 2015). Noni can ameliorate immune function by augmenting antioxidant enzyme functions and reducing lipid peroxidation (Thyagarajan, 2014).

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We also discovered that some genes expression of *S. cerevisiae* was changed after being treated with noni fruit extract, and defected *S. cerevisiae* growth cells, especially in G1 to S transition phases (Hermansyah & Susilawati, 2017). Since corona virus is composed by special DNA fragment, it needs a host for noni extract to bond with active site of the virus. It can be indicated that there is a link between noni and the corona virus. In 2011, Frieman *et al.* reported that use of the yeast-based screen to identify antivirals is rapid and efficient, and could explore a strong functional connection between the PLP (Papain like-Protease)-based yeast assay, the inhibitory compounds, and SARS-CoV biology. According to this finding, there is a possibility for noni extract to restrain infected human body by corona virus, and yeast *S. cerevisiae* as support in the research. Use of budding and fission yeast has been utilized as a model tool for study of plant, animal, and human viruses including the interaction between their cellular proteins with viruses, and they can be used to study cell cycle regulation as well

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as aspects of antibacterial cell death (Zhao et al, 2017). Moreover, if this tool is combined with use of higher eukaryotic system tool, it will become a better and unique set of tools.

Application of *Saccharomyces cerevisiae*

Yeast *S. cerevisiae* is a popular single cell eukaryotic model organism for molecular studies/research and it has been highly conserved from yeast to higher eukaryotic organism. *S. cerevisiae* is not only used to study fermentation for bioethanol production, but also used to study other important aspects including to the study of cellular impacts related to virus-host interactions.

Characteristics of yeast *S. cerevisiae* are 16 chromosomes with genome size 1.2×10^6 bp with at least 5,700 genes, and approximately 4.4% introns. It is easy to handle as growth is with short doubling time, generally recognized as safe organism (GRAS), be able genetically engineered with small genomes to permit genome-wide analysis between virology and cellular functions that would be of benefit to if used in molecular studies (Zhao, 2017). Other characteristics and the advantages of *S. cerevisiae* in research are as follows: well-known genetic and physiology; 2 microns plasmid for expression vector, has a strong promoter, be able to modify post translation, easy and inexpensive cultivation as both are haploid and diploid cells, efficiency in sporulation and mating, available mutant libraries, and production of human heterologous the Secretory Leukocyte Protease Inhibitor (SLPI) which has multiple functions i.e. anti-inflammatory and anti-microbial (Ulfa et al, 2020). The budding yeast *S. cerevisiae* is a very good model for identifying drug candidate from bioresource or natural product with antiproliferative properties (Qaddouri et al, 2011).

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The cell cycle is a series of events involving the growth, replication, and division of a eukaryotic cell. In normal cell, transition progression of cell cycle in each Gap 1 (G1), Synthesis (S), Gap 2 (G2), and Mitotic (M) phases are regulated tightly (Figure 1.7). G1 and S phases are an unbudded form, while G2 and M phases are a budded form. Corona virus has large genome which it is insufficient to use *Escherichia coli*. Therefore, *S. cerevisiae* is the best selection. On the other hand, virus isolates are applied such as diagnostics tool construction, as in vivo models, antiviral therapeutics and vaccines. If the presence of viral genome isolates is limited, viral genomes can be cloned chemically from DNA synthetic.

One essential target of corona virus, papain-like protease (PLP), has many roles in pathogenesis such as producing the replicase proteins required viral replication (Clemente et al, 2020). A yeast-based assay was established for PLP activity, depending on the capability of PLP to induce a clearly slow-growth phenotype when applied in *S. cerevisiae*. Induction of the slowed growth was represented to occur over a 60-hour time course, providing the basis for screening small molecules that restore cell growth by affecting the function of PLP (Frieman et al, 2011).

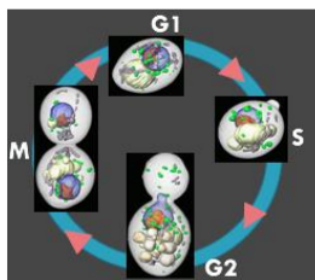


Figure 1.7: Cell cycle of the budding yeast *S. cerevisiae* is tightly regulated in cell growth.
(modified photograph by Hermansyah)

The development of DNA

The structure of double helix Deoxyribose Nucleic Acid (DNA) linked by hydrogen bonds has been facilitated in recombinant technology. DNA transcribed into RNA molecule, translated into protein/ enzyme synthesis has triggered the protocol of read-write-edit genome. Cloning gene generates identical copies of DNA gene sequence. The DNA sequence could be analyzed and identified by the reading technique based upon fragment nucleotide in a DNA molecule). By using CRISPR (Clustered Regularly-Interspaced Short Palindromic Repeats) technology, DNA sequence genome of living organism is easy to alter or edit resulting in modified gene function (Zhang et al, 2012). At the beginning of the 21st century, the synthesis of viral and bacterial genomes, namely poliovirus (2002) or bacteriophage ϕ X174 (2003) and *Mycoplasma genitalium* (2008) or *Mycoplasma mycoides* (2010), respectively became the aim of yeast expansion. *Saccharomyces cerevisiae* became the global attractive project to synthesize all 16 chromosomes-the Synthetic Yeast Genome (Yeast 2.0 or SC 2.0) project (Dixon & Pretorius,

2020). The timeline of the synthesis of viral and bacterial genomes became the concept to chemically synthesis the 16 chromosomes of *S. cerevisiae* (Figure 1.8).



Figure 1.8: The timeline of the synthesis of viral and bacterial genomes became the concept to chemically synthesis the 16 chromosomes of *S. cerevisiae* (Dixon and Pretorius, 2020).

The research about SARS CoV-2 virus has emerged to be the highest priority target of global and international projects. Parts of spike (S), envelope (E) and membrane (M) proteins from the SARS-CoV-2 virus surface coat are necessary vaccine candidate targets. The recombinant co-expression of those proteins in a designed *S. cerevisiae* platform (D-Crypt™) and their self-assembly as virus-like particle (VLP). This multi-antigenic VLP for SARS-CoV-2 has potency to be a scalable vaccine candidate. The VLP is detected by series data as follows: Transmission Electron Microscopy (TEM) data of the SARS-CoV-2, High Performance Liquid Chromatography

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² (HPLC), Dynamic Light Scattering (DLS) and allied analytical data. The study is enabled to develop use of *S. cerevisiae* to produce a potential vaccine candidate against pandemic virus SARS CoV-2 with scalable, cost effective, and simply process (Arora et al, 2020).

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³ Based on the above features, the yeast *S. cerevisiae* was selected to clone, assemble and mutagenize entire *Mycoplasma* genomes, used to design and produce chemically synthesized clone of the virus, SARS-CoV-2, within seven days after accepting synthetic DNA fragments. Since yeast can recombine overlapping DNA fragments in vivo, which helps develop transformation-associated recombinant (TAR) cloning technique (Figure 1.9) (Thao et al, 2020). In-yeast genome rearrangement, DNA recombinant of viral genome and a TAR vector uses one-step delivery of overlapping DNA system. TAR cloning was successfully applied to the mouse hepatitis virus (MHV) that contains Green Fluorescent Protein (GFP) gene. Recombination of viral ORFs and GFP's ORF created by homologous recombination in *S. cerevisiae* was transformed to produce a yeast artificial chromosome (YAC). This YAC has the whole of viral cDNA sequence. In vitro system, the infectious capped viral RNA begins with isolation of the YAC, then linearization of plasmid to provide a DNA template for run-off T7 RNA polymerase-based transcription. Virus rescue is carried out by electroporation of cells, after those virus production and amplification are conducted by culturing the virus with susceptible cells (Thao et al, 2020).

Conclusion

Bioresources have the potential to be utilized as object and model study to overcome COVID-19 pandemic problem. Natural product such as *M. citrifolia* with some efficacy might have the potency to be good drug candidate where further and more detail study is needed. The eukaryotic organism budding yeast *S. cerevisiae* has some characteristics advantages which has emerged as the excellent model organism and tool to develop for virus research. By using *S. cerevisiae* co-expression important part genome of SARS-CoV-2 virus namely Spike protein, Envelope protein and Membrane protein as multi-antigenic virus-like particle, have been applied to develop vaccine candidate.

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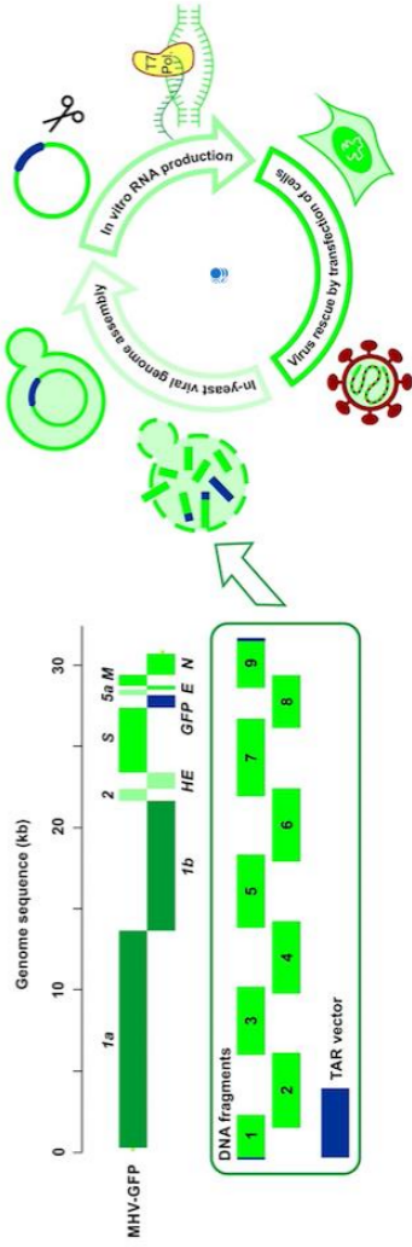


Figure 1.9: Schematic of TAR cloning and virus rescue (Thao et al, 2020).

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