The background of the cover is a collage of natural ingredients. In the top left, there is a piece of ginger root. To its right are fresh green herbs, including what appears to be parsley and mint. In the center, there are several white flowers with yellow centers. On the left side, there is a small white bowl filled with yellow and white capsules. On the right side, there is another small white bowl containing a light-colored liquid. The overall composition is vibrant and emphasizes natural health products.

PREVENTIVE MEDICINE OF COVID-19

TRADITIONAL LOCAL KNOWLEDGE IN INDONESIA AND MALAYSIA

Editors

Yosie Andriani

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Penerbit UMT
Universiti Malaysia Terengganu (UMT)
21030 Kuala Nerus
Terengganu
2022

*PREVENTIVE MEDICINE OF COVID-19
Traditional Local Knowledge in Indonesia and Malaysia*

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PREFACE

The chapter in book is the result of a joint webinar that was held on 20th October 2020 between Institute of Marine Biotechnology (IMB), Universiti Malaysia Terengganu (UMT), Terengganu, Malaysia with other three faculties of three Universities from different Provinces in Indonesia, under Memorandum of Understanding (MoU), Letter of Intent (LOI) and Memorandum of Agreement (MoA) collaborations. These three faculties and universities, namely, the Biosciences and Biotechnology Research Centre (BBRC) - Institut Teknologi Bandung (ITB), Bandung, West Java; Faculty of Sciences and Mathematics (FSM) - Universitas Diponegoro (UNDIP), Semarang, Central Java; and Faculty of Mathematics and Natural Sciences (FMIPA), Universitas Sriwijaya (UNSRI), Palembang, South Sumatera. We would like to thank all contributors from universities in Indonesia and Malaysia for their participation and support for this book: The three universities in Indonesia are namely, Universitas Bengkulu (UNIB, Bengkulu, Sumatera, Indonesia); Universitas Syah Kuala (UNSYAH, Kota Banda Aceh, Sumatera, Indonesia); Universitas Jenderal Soedirman (UNSOED, Purwokerto, Central Java, Indonesia); and three universities in Malaysia are, University College TATI (UC TATI, Kemaman, Terengganu, Malaysia), Universiti Teknologi MARA (UTM, Bukit Besi, Dungun, Terengganu, Malaysia); and International Islamic University Malaysia (IIUM, Bandar Indera Mahkota, Kuantan, Pahang, Malaysia).

This book provides information on COVID-19, which has become a global pandemic and affected the lives more than 3.5 billion of individuals in the world. Through this publication the knowledge on the natural products and bioactive compounds can be used as potential agents for COVID-19 prevention. Besides that, COVID-19 diagnostics approach and application, as well as the prediction of numbers of infected people by prediction models and a mathematical formulation were also proposed to expedite the success in developing the optimal drug delivery strategies to fight this pandemic in the future.

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Some of the chapters in this book were supported by various research grants from Indonesia and Malaysia. Two chapters from UMT were supported by grant from Malaysia, Fundamental Research Grant Scheme (FRGS), Ministry of Health Malaysia (MOH) with vote number 59577 and reference number (FRGS/1/2019/STG06/UMT/02/4). In addition, two chapters from ITB and UNDIP were supported by Indonesia's grant "*Lembaga Pengembangan Inovasi dan Kewirausahaan*" (LPIK)-ITB with project numbered LPIK.PN-6-26-2020 and Ministry of Research and Technology/BRIN Republic Indonesia through "*Penelitian Dasar Unggulan Perguruan Tinggi*" (PDUPT)-UNDIP with project numbered 187-27/UN7.6.1/PP/2021, UNSRI stated that some parts of their chapter content were partially supported by "*Dana Isian Penggunaan Anggaran*" (DIPA) of Public Service from their university.

We hope this collaboration's chapter in book will make its mark as a specialised reference not just for researchers, lecturers and students in Malaysia and Indonesia, but also for people all around the world. This book can be a source of idea and knowledge in research to the treatment or control of COVID-19 and comorbid by using herbal plants and become a source of ideas for alternative methods of prevention of COVID-19 in the future.

INTRODUCTION

This book is divided into three main parts. The first part discusses several strategies to boost our body's immunity by consuming healthy foods like traditional herbs and following healthy protocol such as practicing physical distancing, hand sanitizing and avoiding tight or crowded spaces. Certain side effects that prevent the transmission of infections using PPE are associated not only with previously reported painful skin and mucous reactions, but also include numerous adverse reactions associated with respiratory systems. The study provided some valuable professional health insights to help fellow global medical compatriots who are fighting on the front line to contain the viral outbreak of COVID-19. Furthermore, natural products such as *Morinda citrifolia* and *Saccharomyces cerevisiae*, can be used as an alternative medication, with or without combination with the conventional drugs for COVID-19 patient from mild, moderate, severe and even critical stage as well as recovery stage, as it showed the promising effects. Nevertheless, coastal plants which have potency for preventing this pandemic can be used as a new alternative approach. Furthermore, in the future, preventing COVID-19 can be focused on the coastal plant's bioactive compounds and their perspective role and pathway.

Part II, discusses the contributions of biosensor fields in preventing the novel coronavirus need to be considered. Particularly in the field of aptasensors where the popular methods called the SELEX and non-SELEX methods are still used to find the right and efficient way to produce aptamer with high specificity. In addition, during the COVID-19 pandemic, aptasensor can be a solution to replace the existing test, which is known to have many weaknesses with the presence of mutations in the RNA sequence from COVID-19. The search of the treatment for COVID-19 was at its full speed during the pandemic. Although after the vaccines have finally been discovered, the effort remains relevant. The uses of natural liposomes as an efficacious vaccines' delivery and adjuvants due to their physicochemical properties were suggested. Moreover, how the advancement in *in silico* technology has facilitated the fast identification and characterization of the virus and its potent inhibitors.

Part III, discusses COVID-19 diagnostic approach and its prediction after this pandemic spread globally for one year (since 2019). As 1-year COVID-19 became a global pandemic, the prediction of the numbers of infected people has been continuously developed by introducing various models of predictions. One interesting model which is a combination of the classical models of infectious

disease called SEIR and one popular method under machine learning called Artificial Neural Networks (ANN), have been investigated to predict the confirmation, deaths and recovered cases of COVID-19. Mathematical formulation as proposed in the last topic also helps to expedite the success in developing the optimal drug delivery strategies to fight this pandemic.

Based on the contents of the book, we hope that it will not only be as a source of ideas and knowledge for the educator and researchers, but also be useful to the pharmaceutical industry in developing drugs product for the treatment or control of COVID-19 by using herbs plants in the future. We are grateful to Allah the Almighty for His boundless blessing and all family members for support that has given us strength during the writing this book until the end.

CHAPTER 3

BIORESOURCES UTILIZATION FOR COVID-19 STUDIES: USAGE OF *Saccharomyces cerevisiae* AND NONI (*Morinda citrifolia*) FRUIT IN A RESEARCH

Hermansyah Hermansyah, Dwita Oktiarni, Getari Kasmiarti & Susilawati Susilawati

Bioresources are the sources of biodiversity that has the 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 colourful vegetables and fruits. Advanced technology helps the herb medicines with the 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 the 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 have 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 *Mengkudu* (Figure 3.1). People usually make use of this as traditional medicine and food (Assi *et al.*, 2017; Shalan *et al.*, 2016). Noni plants are 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 (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 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 colours 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 its mechanism (Inada *et al.*, 2017).

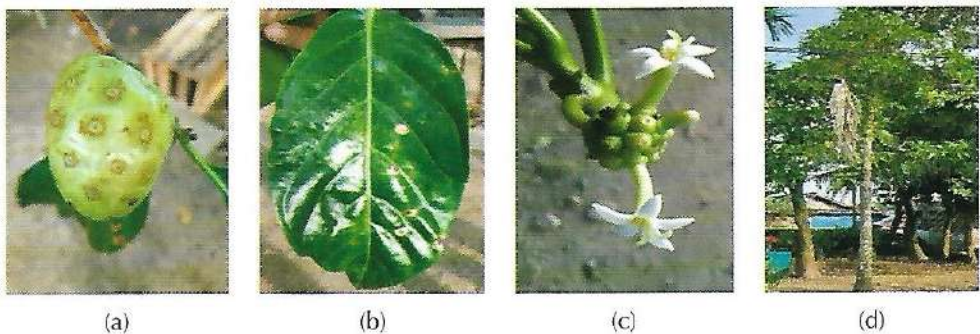


Figure 3.1: *Morinda citrifolia* or noni plant (a) fruit, (b) leaf, (c) flower and (d) tree
Photograph by Hermansyah

The bioactive substances in *M. citrifolia* highly respond to 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 amount 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 are 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).

Coronavirus outbreak emerged in Wuhan, China at the end of 2019. The occurrence of rapid transmission cases and the absence of 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 coronavirus and undergoing treatment at Dadi Hospital in Makassar. Based on this case, there must be strong a correlation between noni plant and coronavirus 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 viruses. 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).

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 coronavirus 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 coronavirus. 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 coronavirus 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 as aspects of antibacterial cell death (Zhao *et al.*, 2017). Moreover, if this tool is combined with the use of a 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 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 percent 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 if used in molecular studies (Zhao, 2017). Other characteristics of *S. cerevisiae* in research are described as follows: available mutant libraries, has a strong promoter, able to modify post translation and produce human heterologous 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).

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 3.2). G1 and S phases are an unbudded form, while G2 and M phases are a budded form. Coronavirus 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 coronavirus, papain-like protease (PLP), has many roles in pathogenesis such as producing the replicase proteins required viral replication

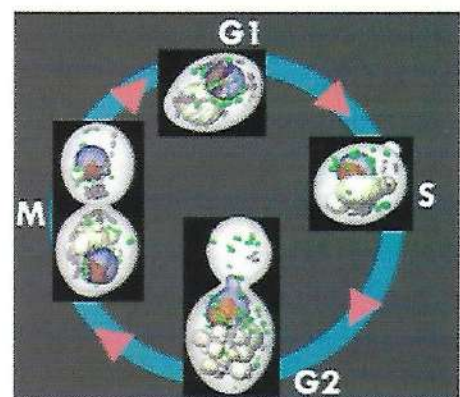


Figure 3.2: Cell cycle of the budding yeast *S. cerevisiae* is tightly regulated in cell growth.

Modified photograph by Hermansyah

(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).

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 engineered 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 3.3).

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 is expressed in a designed *S. cerevisiae* platform (D-Cript™) 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 (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 simple process (Arora *et al.*, 2020).

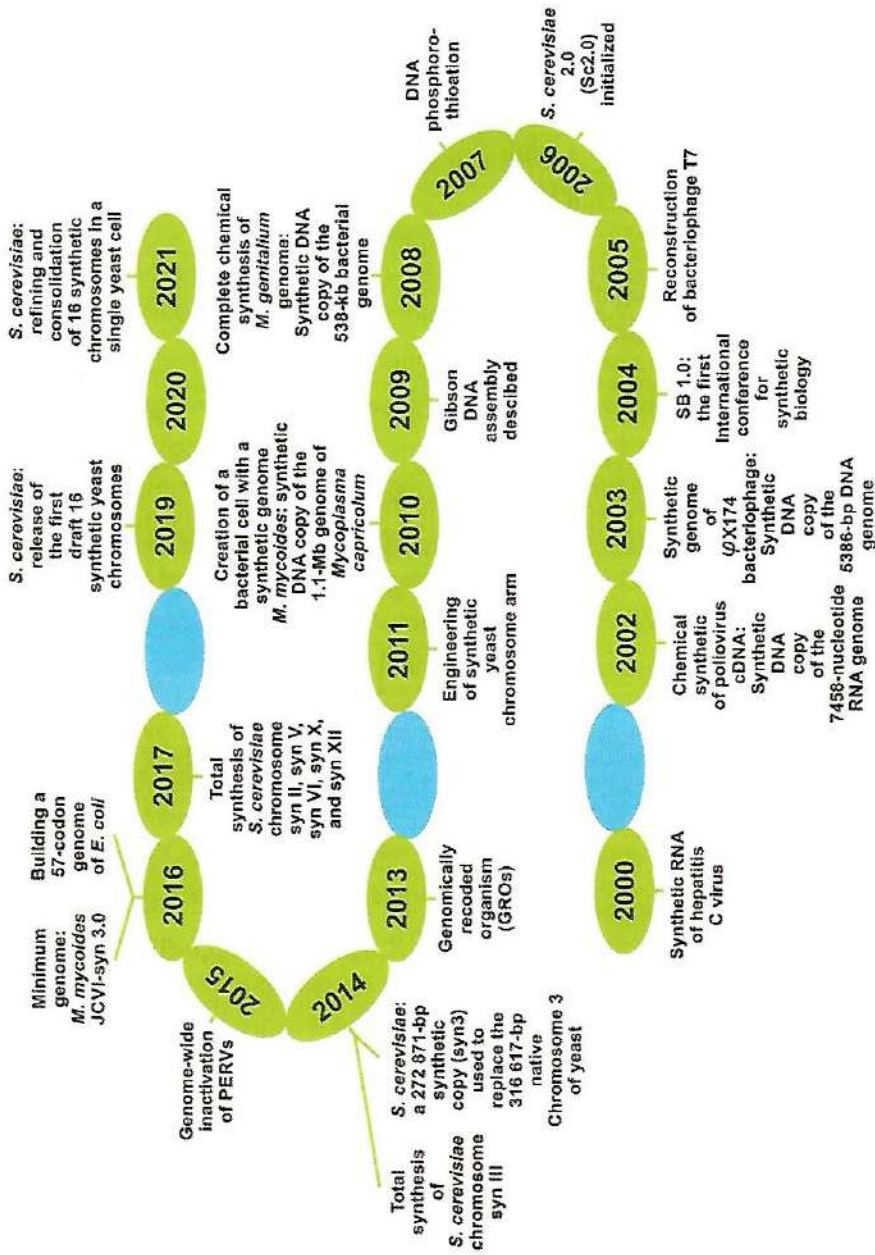


Figure 3.3: The timeline of the synthesis of viral and bacterial genomes became the concept to chemically synthesis the 16 chromosomes of *S. cerevisiae*

Dixon & Pictorius, 2020

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 3.4) (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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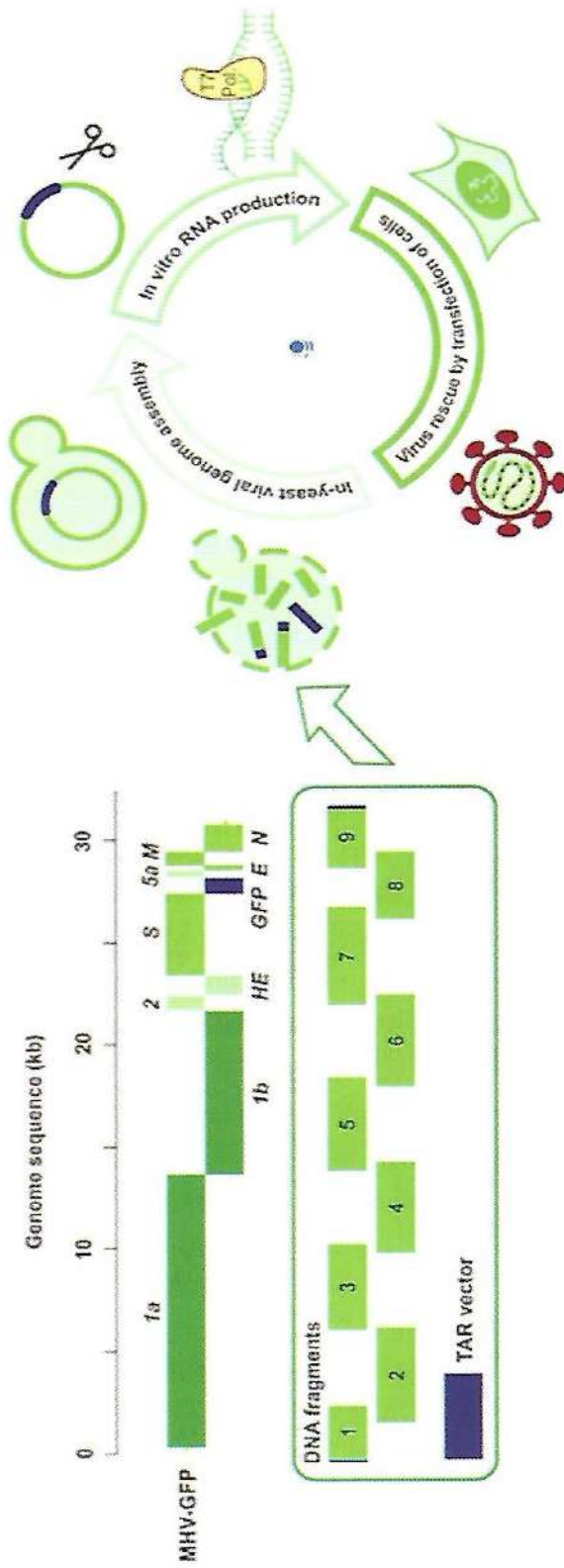


Figure 3.4: Schematic of TAR cloning and virus rescue
 Thao et al. (2020)

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