Journal of Pharmacognosy and Phytochemistry
Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
www.phytojournal.com
JPP 2021; 10(6): 37-49
Received: 16-07-2021
Accepted: 24-08-2021

Aira B. Dacasin
Department of Biochemistry, Faculty of Pharmacy, University of Santo Tomas, Manila, Philippines

Dixie May B. Diagono
Department of Biochemistry, Faculty of Pharmacy, University of Santo Tomas, Manila, Philippines

Paula Kate N. So
Department of Biochemistry, Faculty of Pharmacy, University of Santo Tomas, Manila, Philippines

Von Rovic L Bautista
Department of Biochemistry, Faculty of Pharmacy, University of Santo Tomas, Manila, Philippines

Michael Lorenzo B Bucu
Department of Biochemistry, Faculty of Pharmacy, University of Santo Tomas, Manila, Philippines

Ruel Valerio R De Grano
Department of Biochemistry, Faculty of Pharmacy, University of Santo Tomas, Manila, Philippines

Gracia Fe B Yu
Department of Biochemistry and Molecular Biology, College of Medicine, University of the Philippines - Manila, Philippines

Paolo Robert P Bueno
Department of Biochemistry and Molecular Biology, College of Medicine, University of the Philippines - Manila, Philippines

Corresponding Author:
Aira B. Dacasin
Department of Biochemistry, Faculty of Pharmacy, University of Santo Tomas, Manila, Philippines

The potential use of virgin coconut oil as an adjunctive treatment for COVID-19: A review

Aira B. Dacasin, Dixie May B. Diagono, Paula Kate N. So, Von Rovic L Bautista, Michael Lorenzo B Bucu, Ruel Valerio R De Grano, Gracia Fe B Yu and Paolo Robert P Bueno

DOI: https://doi.org/10.22271/phyto.2021.v10.i6a.14254

Abstract
This review summarizes the background of *Cocos nucifera*, the benefits of the isolated virgin coconut oil (VCO), such as its potential as an adjunctive treatment for COVID-19, and its pharmacological effects, including antiviral and anti-inflammatory properties that could be applicable for therapeutic purposes against viral diseases. Observational studies, randomized, double-blind controlled intervention trials, and nonrandomized studies comprise this review that served as a basis. Consequently, from these summarized reports, the substances present in the VCO exhibit antiviral and immunomodulatory activity adjunct with antiviral drugs, which could prevent host cell infection and viral infection replication or reduce the inflammatory effects of COVID-19. Even though there are several studies of VCO in relation to its pharmacological properties, no recent studies have considered the implementation of the secondary metabolites present in virgin coconut oil as an adjunct to COVID-19 treatment. Therefore, further human clinical and observational studies for VCO are needed to suffice the need for evidence in regard to its potential use as an adjunctive treatment against COVID-19.

Keywords: Virgin coconut oil, SARS-CoV-2, coronavirus disease, adjunctive treatment, *Cocos nucifera*

1. Introduction

The emergence of the 2019 novel coronavirus, known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has initiated a pandemic of coronavirus disease (COVID-19) worldwide [1]. Coronaviruses, or known as CoVs, are a large family of viruses that cause respiratory infections in humans. Through which it will start from a common cold to more severe conditions, including severe acute respiratory syndrome (SARS). Furthermore, CoVs have high mortality rates and were first detected in 2003 [2]. According to the World Health Organization, as of 18 July 2021, there have been reports that more than 190 million people have confirmed cases of COVID-19 globally, with at least 4 million people confirmed deaths [3]. For now, the search for identifying alternative treatments for the novel coronavirus disease is still ongoing. Through this, scientists were driven to explore more natural plant-based therapeutics against COVID-19 [4].

Virgin coconut oil (VCO) is an edible oil isolated from the milk of fresh and the kernels of the matured coconuts from the *Cocos nucifera* [5]. It is widely used as cooking oil and in some food industries, including baking products and confectionery [6]. VCO is also known for its pharmacological properties, including antiviral, antioxidant, anti-stress, antimicrobial, and anti-inflammatory [7, 8]. Therefore, it has various health benefits, such as having the potential to treat gastrointestinal problems, injuries, and swelling [9].In addition to that, it inhibits cancer-causing agents [10] and *Candida sp* growth, which is responsible for fungal infection [11] and lastly, VCO has antioxidant activities that do not adversely affect serum lipid levels [12].

In the Philippines, scientists were eyeing VCO as an effective adjuvant treatment for COVID-19 patients. Based on *in vitro* studies for the immunomodulatory properties of VCO, results showed that it suppresses inflammatory cytokines [13].Moreover, it has been reported that patients having severe COVID-19 symptoms were characterized to have cytokine release syndrome, a type of inflammatory response associated with the high levels of pro-inflammatory markers that play a role in mortality and morbidity of COVID-19 [14]. VCO was used in pharmacological and biological studies that were being analyzed qualitatively and quantitatively, based on its biochemical markers to the probable cases of COVID-19 patients [7]. It has been shown that VCO can be used as an adjunct supplement because of its properties, including antiviral and immunomodulatory. This review aims to highlight the importance and potential of the virgin coconut oil isolated from *Cocos nucifera* as possible adjunctive therapy for COVID-19 patients.

Thereby, this review comprises of summarizing the background of *Cocos nucifera*- the source of VCO, the benefits of VCO, including its potential as adjuvant therapy for the COVID-19 patients, and its pharmacological effects, including antiviral and anti-inflammatory properties that could be useful for therapeutic purpose against viral diseases, such as COVID-19.

2. SARS-CoV-2 caused coronavirus disease (COVID-19)

2.1 Epidemiology

COVID-19 was declared as a pandemic on 11 March 201 by the World Health Organization (WHO). They pointed out over 118,000 coronavirus illnesses in over 110 countries worldwide, with a mortality rate of 2.34%, which is still further spreading globally [15]. This disease has caused a sudden increase of patients being hospitalized for pneumonia together with multiorgan illness. Although there may be times when the infection may be asymptomatic, there is a large scope of symptoms, from mild symptoms of upper respiratory tract infection to life-threatening sepsis [16]. The Severe Acute Respiratory Syndrome-Coronavirus-2 or SARS-CoV-2 is the COVID-19 virus that was originally from Wuhan, China, where it was first transmitted from an animal host to humans [17]. Epidemiologists suggested that the outbreak initially started from seafood markets where wild animals were sold for human consumption. It was discovered that the infective virus is the new seventh member of the coronaviridae family based on the viral structural and genomic studies of the samples from infected individuals [18].

Based on the WHO (2021) reports, as of 19 July 2021, there have been 1,507,755 confirmed cases of COVID-19 in the Philippines, and there are 26,714 deaths and 1,400,000 recoveries. Despite the fact that approximately 12,703,081 vaccine doses have already been administered in the country and more than 3.65 billion vaccinated worldwide, there is still a need for further research on the said disease since recent updates have shown that the virus is continuing to mutate and creating new variants that can potentially be resistant to some COVID-19 vaccines [19].

2.2 Characterization of the virus

SARS-COV-2 is part of a family of coronaviruses, which are large, enveloped, positive-stranded RNA viruses with a nonsegmented RNA genome of approximately 26-32 kilobase size known for infecting avian and mammalian species [20].Their name comes from their crown-like appearance of having a spike-like projection of glycoproteins on their surface when seen under an electron microscope. The coronavirus genome encodes several structural and nonstructural proteins. Like other coronaviruses, SARS-CoV-2 has four structural proteins known as the coronavirus spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein which is a protein associated with an envelope. The virus uses these structural proteins for membrane fusion, host infection, viral assembly, morphogenesis, and release of viral particles; the trimeric S protein is the essential protein that facilitates viral entry into the cell. Conversely, nonstructural proteins are utilized for viral transcription and replication. [21] SARS-CoV-2 is known for its rapid mutation, frequent recombination, and ease in crossing species barriers, causing frequent novel-cross-species infections [22].

2.3 Pathophysiology

2.3.1 Transmission

COVID-19 can be spread from person to person mainly through respiratory droplets or when an infected person breathes out small particles containing the virus. These particles or droplets may also contaminate surfaces and infect other people who come in contact with the same surface [23]. The virus may also be transmitted through the fecal-oral route since it has been confirmed that the virus can live in feces, sputum, and pharynx. It takes about 5.2 days for the COVID-19 median incubation period from exposure to symptoms onset, whereas most patients experience viral symptoms after 11.5 to 15.5 days. A quarantine period of a minimum of 14 days is recommended to limit the transmission of the virus from the exposed individual [24].

2.3.2 Symptoms

Since SARS-CoV-2 is a respiratory virus that primarily infects the respiratory tract and lung cells, most symptoms are mostly linked to respiration processes. Some of these symptoms include but are not limited to shortness of breath, cough, runny nose, sore throat, diarrhea, body aches, and vomiting. Moreover, this virus can also cause a loss of smell and taste. In more adverse cases, people infected with COVID-19 may experience acute respiratory distress syndrome, severe inflammation, multiple organ failure, and even death [25]. People with underlying chronic health conditions as well as elderly individuals aged 60 years old and above are more susceptible to having the disease. Moreover, it was revealed that the most distinctive comorbidities of SARS-CoV-2 infection were diabetes mellitus and hypertension, as depicted from the clinical data collected from non-survivor patients [26].

2.3.3 Pathogenesis mechanism

For the virus to infect an organism, it must first find a way to enter its host cells to further its viral infectivity. SARS-CoV-2 enters the host cell, such as the lung cell, and binds to a cell surface receptor, specifically the angiotensin-converting enzyme 2 (ACE2) receptor using its S protein [27]. The host proteases, one of which is trans-membrane protease serine 2 (TMPRSS2), subject this S protein to proteolytic cleavages in two sites located at the boundary between the S1/S2 site. The primary function of the S1 subunit is to bind with the host cell surface receptors, while the function of the S2 subunit is to mediate membrane fusion in order to release the fusion peptide (FP) into the host cell. The E protein is known as the small membrane protein that functions in membrane permeability of the host cell and virus-host cell interaction as well as virus assembly. The central organizer for coronavirus assembly is the M protein. In contrast, the N protein directly attached to the ssRNA makes it capable for the virus to hijack the host cell and use it as its virus factory [28].Once the RNA enters the host cell, it duplicates its RNA inside vesicles. Some of these copies are used to make more viral proteins, while others are packed as virus particles that will go out and invade other cells of the host. The virus particles fuse the cell membrane, allowing them to exit and infect more cells, ultimately causing the disease [29].

2.4 Treatment options

As of today, there are still no promising antiviral agents that have been developed to battle SARS-CoV-2. The currently available drugs are still being investigated, and the different kinds of vaccines are still being monitored as they are disseminated globally. Several therapeutic strategies can be used against COVID-19, and it is essential to know these kinds of treatments to know which options to consider.

2.4.1 Antiviral drugs
2.4.1.1 Remdesivir
Remdesivir is known as an experimental drug that was initially developed for the treatment of Ebola virus-infected patients. This adenosine analog interfered with the synthesis of new viral RNA via chain termination and showed antiviral activity against many RNA viruses, including the SARS-CoV [30]. In human airway epithelial cells and cell culture, it was demonstrated that remdesivir could efficiently inhibit MERS-CoV and SARS-CoV-1. This drug has recently been discovered to be active against SARS-CoV-2 in cells [31].

2.4.1.2 Chloroquine and hydroxychloroquine
Chloroquine and hydroxychloroquine are used as antimalarial drugs showing antiviral and anti-inflammatory properties against SARS-CoV-2 in *in vitro* studies. These drugs interfere with the chemical environment of human cell membranes, which prevents the virus from entering inside the cells [32].However, *in vitro* activity cannot be interpreted as clinical activity against COVID-19 since it may not necessarily work inside the human body [30].

2.4.1.3 Ivermectin
Based on an *in vitro* study, Ivermectin, an FDA-approved anti-parasitic drug, showed inhibition against the replication of SARS-CoV-2. This drug explicitly inhibits host importin α/β transporter protein, which prevents translocation or shuttling of the SARS CoV nucleocapsid protein from the cytoplasm to the host cell's nucleus, ultimately disrupting the propagation and survival of the virus [33].However, further study is needed in order to determine its efficacy in combating COVID-19 in humans.

2.4.2 Immune modulators
2.4.2.1 Tocilizumab
Tocilizumab is known as a recombinant anti-human interleukin-6 receptor monoclonal antibody that inhibits interleukin-6 (IL-6). It is an indicated treatment for rheumatoid arthritis, but it may be repurposed against COVID-19 since it may combat cytokine release syndrome [34]. Based on previous studies on severe SARS-CoV-2 patients, these people have high amounts of inflammatory cytokines, leading to multiorgan failure and systemic inflammation. Since IL-6 is an essential substance in cytokine syndrome, tocilizumab can block IL-6 and reduce the severity of the disease in COVID-19 patients [30].

2.4.2.2 Convalescent plasma
Convalescent plasma is blood plasma collected from patients who have previously recovered from an infection. Those who have recovered from COVID-19 develop antibodies against SARS-CoV-2, which can be given to COVID-19 patients in order to boost their ability to fight the virus since these neutralizing antibodies may provide immunity against the disease. Convalescent plasma may work best for patients earlier in the condition, of course, and is currently being provided for hospitalized COVID-19 patients [35].

2.4.2.3 Corticosteroids
Since the 1980s, corticosteroids have been used to treat acute respiratory syndrome (ARDS). The two leading causes of COVID-19 are pro-inflammatory cytokines overproduction and cytokine dysregulation. As an anti-inflammatory agent, corticosteroids may be used to reduce the body's inflammatory response to COVID-19 [36].According to the WHO guidelines, it is strongly recommended to use corticosteroids such as dexamethasone in patients with critical COVID-19, especially those requiring respiratory support, in order to increase the chances of survival of the patients [37].

2.4.3 Vitamins
2.4.3.1 Vitamin C
Vitamin C, also known as ascorbic acid, is an essential water-soluble nutrient that plays a wide variety of roles in the immune system, including the T-lymphocytes development and maturation and the promotion of chemotaxis of leukocytes.[38] Moreover, it is a free radical that influences cellular immunity and has anti-inflammatory properties. Vitamin C can lessen the reactive oxygen species (ROS) and inflammation by attenuating NF-KB activation. Since SARS-CoV-2 downregulates the expression of type-1 interferons, which the host uses as a primary antiviral defense mechanism, ascorbic acid does upregulate these host defense proteins [39].

2.4.3.2 Vitamin D
Vitamin D is a fat-soluble steroid hormone precursor that has a vital role in modulating the immune response without triggering an immune overreaction, such as the so-called cytokine storm, which severe COVID-19 illness is highly associated with [40]. A person deficient in vitamin D may increase the chance of having COVID-19 and may also worsen it. It appears that most COVID-19 patients have lower levels of vitamin D, which is why it is highly recommended that vitamin D supplementation be administered in order to boost immunity and reduce human mortality against the said disease. Furthermore, previous studies have also suggested that vitamin D intake can help protect the respiratory epithelium of a person from pathogenic invasion, making it less likely for SARS-CoV-2 to cause an infection [41].

2.4.3.2 Vitamin E
Vitamin E is a fat-soluble compound and is a lipid component of biological membranes. Individuals who are immunosuppressed and have chronic ailments, especially the elderly, are more prone to getting the virus due to the deterioration of their immune system as they age. Vitamin E remedies this by enhancing T lymphocyte-mediated immune function in response to IL-2 and mitogens [38]. With selenium supplementation, vitamin E may increase an individual's resistance to respiratory infections such as SARS-CoV-2 [41].

2.4.4 Vaccines
Over 300 vaccines have been developed by the scientific community eleven months after the emergence of the SARS-CoV-2 virus. Vaccine development usually takes about three to nine years, but with the pace that COVID-19 vaccines have gone through, their phase one trials can go about in only six months. Of the clinical trials that different companies presented in terms of their vaccines, most have shown to be successful in protecting individuals from the virus as well as reducing its further spread. Although numerous studies have emerged regarding the virus characterization, there are still a lot of unanswered questions about the disease it produces. As a result, different technological and conceptual strategies have been done in order to create these COVID-19 vaccines.[42] There are currently 13 different types of vaccines against COVID-19. These include protein-based subunit, RNA, viral vector replicating as well as nonreplicating, DNA, inactivated virus, virus-like particles, live-attenuated virus, viral vector replicating + antigen-presenting cell, viral vector

nonreplicating + antigen-presenting cell, live-attenuated bacterial vector, bacterial vector, and cell-based vaccines with the majority being protein-based subunit vaccines [43]. The safety of these COVID-19 vaccines is crucial in order for them to be trusted and accepted worldwide. Although the efficiency rates presented for these vaccines are outstanding, the data up to date are too small in order to address the adverse events that may eventually come up. Essentially, everyone is encouraged to vaccinate themselves because it is safe to build protection against the virus and provide immunity after complete vaccine administration [44].

Aside from all the treatments presented, herbal medicines and natural products such as virgin coconut oil are observed to have antioxidant, anti-inflammatory, antiviral, and antifungal properties, which could benefit COVID-19 patients [45]. VCO contains a wide variety of phytochemical compounds capable of disintegrating the virus envelope, preventing the viral proteins in binding to the host membrane, and inhibiting the late maturation stage in the virus replication cycle [7]. Further information will be discussed regarding its general information, phytochemical study, and effectiveness in battling COVID-19.

3. *Cocos nucifera*

The coconut tree, known for its scientific name as *Cocos nucifera*, is considered one of the essential fruit trees in the world. These trees can be found in the tropical as well as subtropical regions, including in the Philippines. Furthermore, it has been cultivated due to its multiple uses as it possesses nutritional and medicinal value, and with that, it is also the reason it is often called the “tree of life.” [46] It also produces various products, one of which is developing medicines against certain diseases and some industrial products. VCO, one of the products that come from coconut, has been part of the daily life of people due to its numerous medicinal properties. These include anti-inflammatory, analgesic, antipyretic, antioxidant, anti-stress, and antimicrobial properties [8]. It has also been a significant source of dietary fat and is completely non-toxic to humans [47].

The Philippines has been known as the leading coconut-producing country globally and is followed by Indonesia, India, Sri Lanka, Thailand, and Malaysia [8]. There are various factors as to why these countries are considered an ideal location for VCO propagation. One of the reasons these areas are considered very favorable for the growth of coconut is the average rainfall per year, sandy soil sunlight, and humidity [48].

3.1 Taxonomy

- Kingdom: Plantae
- Taxonomic Rank: Species
- Common Name: Coconut palm
- Taxonomic Hierarchy:
  - Kingdom: Plantae
  - Subkingdom: Viridiplantae
  - Infrakingdom: Streptophyta
  - Superdivision: Embryophyta
  - Division: Tracheophyta
  - Subdivision: Spermatophytina
  - Class: Magnoliopsida
  - Superorder: Lilianae
  - Order: Arecales
  - Family: Arecaceae
  - Genus: *Cocos* L.
  - Species: *Cocos nucifera* L.
- Geographic Information:
- Geographic Division: Caribbean, Oceania, North America
- Jurisdictional/Origin: Continental US, Introduced; Caribbean Territories, Introduced; Hawaii, Introduced

3.2 Morphology

Cocos nucifera trees have this distinct smooth, columnar, light grey-brown trunk having 30 to 40 cm as its mean diameter. The trunk is usually slender and can either be leaning or curved. The tree is crowned with terminal leaves that are feather-shaped, measuring 4 to 7 cm long and 1 to 1.5 cm wide at the broadest, and is thornless. The fruit is roughly ovoid, measuring 5 cm long and 3 cm wide. It comprises a thick fibrous husk surrounding a slightly spherical nut with a hard, brittle, and hairy shell. The nut itself measures 2 to 2.5 cm in diameter and 3 to 4 cm long. Usually, at one side of the nut, there can be three sunken spots of softer tissue. The nut is hollow, with the shell’s interior surrounded by a white fleshy layer called the meat, which contains a partially filled watery liquid called coconut milk [49]. The meat of the *Cocos nucifera* during immaturity is soft and jelly-like but becomes firm with maturity. Coconut milk is originally abundant when unripe but gradually gets absorbed during the ripening process. The coconuts are green or yellow at first, depending on their variety but eventually turn brown as they mature [50].

3.3 Growth, cultivation, and propagation

The growth and cultivation of the coconut greatly depend on the soil type, land slope, and sufficient rainfall distribution. It has been reported in some studies that it grows well on different soil types, including on the well-drained loamy, sandy, and clayey soil where water and air can circulate [47, 51]. It is preferable in soils with different primary macronutrients contents, including nitrogen, potassium, and phosphorus, along with secondary macronutrients such as sulfur, calcium, and magnesium; and lastly, with the micronutrients of chlorine and boron [52]. It also prefers less diurnal variation between day and night; however, it cannot tolerate extreme temperatures [51]. Moreover, the growth of the coconut also favored a year-round warm and humid climate, which can only occur in tropical countries. An evenly distributed rainfall of 1,500-2,500 mm per annum, with a 27ºC as its mean annual temperature, and at least above 60% of the relative humidity could provide an ideal climatic condition for the effective growth and yield of the coconut palm [46]. With that good climatic condition, one coconut palm will be able to produce 12-16 bunches of coconuts per year, and each bunch has 8-10 nuts [47].

Furthermore, 7-8 months of seedlings from fully mature fruits were usually used to transplant for cultivation. For about 16 weeks, nuts are planted in the nursery. Usually, 70-150 coconut palm trees per hectare are planted; as for with a 10 m of triangular spacing, 115 coconut palm trees per hectare; and for group plating, 3-6 coconut palm trees planted that are 4-5 m apart [47]. It is much more desirable to transplant the seedlings during the rainy season. During its first three years, seedlings are watered 16 liters of water per tree during drought, twice a week. Female flowers are set for 12 months, and usually, it takes 8-10 months for a fruit to mature, yielding 60-100 nuts per tree. A coconut tree has the capability to produce at least 10,000 nuts in its lifetime.

3.4 Philippines as the leading coconut-producing country

Coconut has been one of the most important crops and a major export of the Philippines. It contributes 3.6% of the country's gross value-added (GVA) in agriculture, followed by banana, corn, and rice [53]. The reason why the country still stays as a top producer and exporter of coconut worldwide [54]. Hence, the exports of coconut products have become the nation's prime foreign exchange earner [51]. It is also the largest employer of agricultural land and labor in the Philippines [55]. Sixty-eight provinces are considered coconut producers out of 81 provinces of the country [56].

Three hundred forty million coconut trees occupy the 3.502 million hectares of the Philippines' cultivable lands [51]. Davao Region is a top coconut producer with about 497.62 thousand metric tons output or 15.8% of the total coconut production. Next is the Zamboanga Peninsula, with 14.2%, and Northern Mindanao, with 13.7% shares [57]. However, as of January to March 2021, coconut production has declined to 3.14 million metric tons or decreased 0.8%, from the 3.17 million metric tons in the same quarter of 2020 [57].

3.5 Isolating and processing virgin coconut oil from *Cocos nucifera*

The coconut oil source isolated from the coconut fruit has two different types, including (1) coconut oil that is being acquired from the dry coconut flesh and (2) VCO that is obtained from fresh coconut flesh [8]. Furthermore, VCO can also be procured directly from the fresh comminuted coconut meat grated, granulated, chopped, and even from coconut milk and its residue [58]. There are various techniques and processes through which one can obtain VCO from coconut, as seen in Figure 1. The quality and quantity of the final VCO depend on the processing techniques employed for extraction.

In the production of the VCO, three stages need to be taken into account, which are (1) pre-processing, (2) processing, and (3) post-processing stage [8]. The pre-processing stage includes all steps performed prior to opening the fresh coconut, such as harvesting, collecting, and even husking nuts. Then, these coconuts will be transported from the farm to the VCO processing site through which it can be either in the factory or home and lastly for the selection for its daily processing [59]. Next is the processing stage, where the opening of the fresh coconut occurs until the final recovery of the VCO. There are eight ways of processing the VCO, as shown in Figure 1, and it is based on the desired quality of the oil.[58] Moreover, each technique can be classified based on the used precursor form of the coconut. The production of VCO from the fresh coconut meat comprises three different types of a fresh drying process or high pressure expelling process: the wet milling route, the desiccated coconut route, and the grated coconut route; as well as the low-pressure method or the fresh-dry-low-pressure extraction technique. The milk extraction as the precursor can be divided into two categories: coconut milk and its residue. The coconut milk consists of the modified kitchen method, modified natural fermentation method, and centrifuge method. As for the coconut milk residue, it is the bawalan-masa process. And lastly, the post-processing stage includes all the techniques that are performed in order to improve the quality of the obtained VCO. These techniques include oil drying, which removes the moisture content, aging, the sour smell, and fine filtration, which removes the fine residue.

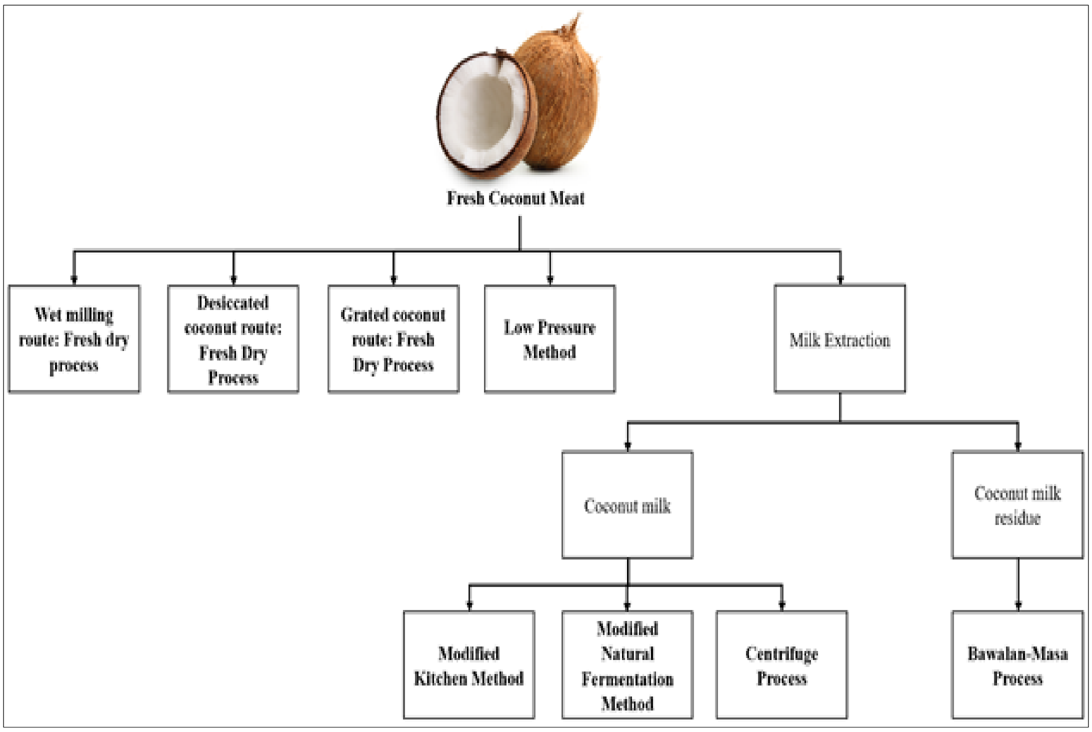

Fig 1: The various methods for processing VCO [58]

3.5.1 Fresh coconut meat

3.5.1.1 High-pressure expeller process (Fresh dry process)

One of the traditional processes of isolating oil from the coconut is through the use of high-pressure expellers. Unlike any other extraction process, the high-pressure expeller method can quickly dry the grated, ground, or even milled form of the coconut meat and be immediately expelled so there could be no deterioration of the meat. Thus, it will produce a very high-quality oil that is suitable for human consumption [58]. In addition, the high-pressure expellers must be stainless steel-made and have a built-in cooling system in its worm shaft in order to prevent the rising of temperature that will cause the oil to turn a yellow color. There are three different types of high-expeller methods-the wet milling route, the desiccated coconut route, and the grated coconut route. They are categorized based on the mode of preparation of kernels before their drying.

3.5.1.1.1 Wet milling route
For this type of route, the de-shelled meat of the coconut is washed with an abundant amount of water. Next, it will be milled. The coconut meat will then be dried at 75ºC; afterward, it will undergo extraction utilizing the screw-type press to produce VCO and coconut flakes [60]. Its advantages are as follows: it creates a VCO full of protein, and the by-product can be used as medium fat coconut flour, it uses a mechanical type of equipment in processing the oil, and it has a long shelf-life that is about one year and more [58]. While its limitation, it can be produced in an operation that is a village-scale plant.

3.5.1.1.2 Desiccated coconut route
This route consists of various processes, including washing, grinding, blanching, and drying the coconut meat. Using a conveyor-type hot air dryer having three diminishing temperature levels, e.g., 100ºC, 85ºC, and 65ºC, the grounded meat will be dried until it reaches a moisture content level of 2.5-3% [61]. Moreover, even though the desiccated coconut products are not acceptable when it comes to their quality standards in terms of their color as well as their microbial content, they can be processed into a high-quality VCO. Its advantages are similar to the wet milling route, but its limitation is limited to a medium-scale plant [58].

3.5.1.1.3 Grated coconut route
The grated coconut route is quite similar to the desiccated coconut route; however, it is different in such a way that it only requires fewer processing steps and equipment.[60] It also has the same advantages as the other two routes, but its limitation can only be done in a micro-scale plant operation [58].

3.5.1.2 Fresh-dry low-pressure extraction method
This method, also called the intermediate moisture content technique [61]. Utilizes a low pressure of approximately 460 psi. With that, it can isolate oil from seeds and nuts with a moisture content maintained between 10-13%. Similarly, VCO can also be extracted from finely grated and dried coconut meat if only the moisture content level is maintained into its optimum range. The grated coconut kernels can be dried either through an indirect air drying or sun drying, and it is placed in cheesecloth-made bags. Its isolation process is usually done in a bridge press for the easy removal of the residue. While the cheesecloth serves as a filter, the obtained oil will consist of a minimal amount of fine kernel particles.

3.5.2 Coconut milk from milk extraction
3.5.2.1 Modified kitchen method
Bawalan & Chapman (2006) stated that the modified kitchen method follows the process of boiling the coconut milk isolated from freshly grated or even the comminuted coconut meat upon adding or not of the water to produce the coconut oil [58]. The oil produced using this method is in dark yellow with a concise shelf life through which it usually results in rancid within three to five days. The process of its extraction and preparation includes selecting nuts, splitting, and grating. It will undergo two extraction processes that can be done manually or through the machine, mixing the first and second milk extracts. Afterward, the mixed extracts will be settled, then separating the coconut cream and its coco skim milk. The coco cream will be slowly heated, then separation of the oil and latik will be conducted. Oil drying will be done in order to ensure that the residual will be removed and final filtration of oil through a muslin cloth. VCO may now be stored in stainless steel containers and poly-lined drums.

3.5.2.2 Modified natural fermentation method
The modified natural fermentation method for producing VCO only relies on the natural separation in coconut milk without any addition of fermentation. According to Bawalan & Chapman (2006), it only allowed the coconut milk mixture to stand for more than 10 hours under its favorable conditions [58]. The oil will then separate naturally from the water as well as into its protein content; hence no other substance such as yeast, enzyme, or microorganism is needed for this method. It only requires the lowest labor; however, if it is not adequately controlled, it could result in oil with a sour smell with a relatively higher free fatty acid content which cannot be considered as VCO. Furthermore, it has the same method as the modified kitchen method. Its process only consists of settling the coconut milk mixture, then separating the oil and fermented curd layers. It will then undergo oil drying, filtrating the oil, heating the fermented curd, and it can now be stored.

3.5.2.3 Centrifuge method
It has been reported that the centrifugation method produces a high yield of VCO as compared to other traditional processes such as fermentation [62]. Hence, this method can be applied at the industrial level. Moreover, the best centrifugation speed is at 12000 rpm as it produces the best separation compared to the other centrifugation speeds. Certain factors can affect the yield of VCO to become unstable, including the temperature of the centrifuge machine. Therefore, the centrifuge must be exposed to room temperature for about 15 minutes prior to continuing the said experiment. Otherwise, the coconut milk will be solidified when immediately placed in the centrifuge from the temperature set to 20ºC-25ºC. Furthermore, exposing the coconut milk for a long time can cause oxidation to occur, which will result in the rancidity of the coconut milk. Among those mentioned methods, it also produces the best quality of VCO with the sweet coconut aroma if done in a two-stage centrifuge process [58].

3.5.3 Coconut milk residue from milk extraction
3.5.3.1 Bawalan-masa process
The Bawalan-Masa Process is considered as a hybrid of both fresh dry and fresh-wet processes. The VCO produced from this method is very light in texture and has a very mild coconut scent [61]. The source for this VCO isolation method is coconut milk residue, and it represents the weight of the freshly grated coconut meat, which is approximately 25-50%. As for its process, the residue is blanched then dried in a mechanical dryer in order to reach the desired moisture content. Specific equipment produces the resulting VCO and low-fat, high fiber coconut flakes from defatting the dried residue under controlled conditions. Then the coconut flakes can be reused by re-drying and grounding it in order to produce the coconut residue flour.

3.6 Applications and health benefits of virgin coconut oil

There has been a long history of usage of VCO, as well as some various studies that elucidate more of its uses that can be either consumed by humans and even animals or can be transformed into valuable products to be commercially produced. Its purposes can be edible and inedible as it performs many functions. The edible applications for this VCO are as follows: (1) it can be a source of fat in the infant foods as it can be digested and absorbed easily; (2) it can be used as a cooking and frying oil in order to enhance the flavor as well as, increase the shelf-life of food; and (3) it can be applied as an ingredient in the confectionery including candy bars.[58] The main reasons for its various applications include its numerous functions. It can provide specific nutritional requirements, enhance the flavor of certain foods, and serve as an essential source of energy in the diet. Its inedible application can produce biodegradable detergents and other cleaning products, for cosmetics, toiletries, and synthetic resins production and plasticizers for the plastic product. That being said, it is indeed that there are emerging major uses and distinct applications of VCO, such as nutraceuticals and functional food, an oil base for several skincare products, as well as hair conditioner [58].

Apart from its various applications, VCO also provides health benefits that could reduce some risks of certain diseases, including chronic disease. It has been reported that VCO has similar beneficial effects in mother’s milk that can give babies an immunity to disease due to its medium-chain fats from C8 and C12, similar to breast milk [63]. Furthermore, it protects arteries from atherosclerosis and cardiovascular diseases as it possesses anti-inflammatory, antimicrobial, and antioxidant properties that work together to prevent the said diseases.[64] In addition to that, VCO has the capability to inhibit the action of cancer-forming substances due to its anticarcinogenic effect [10]. Although this only comprises the majority of health benefits of VCO, further studies are still needed for the VCO to provide confirmatory evidence for its other potential to improve lives and give benefits to humans.

4. Phytochemical study of virgin coconut oil

4.1 Chemical composition and its nutritional value

Considering the extraction process of VCO that only involves no or little heating, its biologically active substances lost during the refining process can remain entirely in the oil. VCO and RBD oil (Refined, Bleached, and Deodorized) provide the same essential chemical properties. The substances present can have quantities that can provide nutritional and health benefits, including preventing and reducing chronic diseases. There are biologically active substances that can be seen occurring from *Cocos nucifera*, and among the most important stable biologically active substances is a fatty acid in the triglyceride form.[65] Moreover, other biologically active phytochemical substances found in this plant grow an interest worldwide in human health. Listed below are the phytochemical content of VCO.

Table 1: Phytochemical profile of the virgin coconut oil

Phytochemical Content	References
Tocopherols	[65]
Tocotrienol	
Phytosterol	
Phytostanols	
Flavonoids and other polyphenols	
Phospholipids	
Medium Chain Triglycerides (MCT) • Lauric acid (53.70%–54.06%) (48.40%-52.84%) • Stearic acid (2.65%–12.10%) • Lactic acid bacteria • *Lactobacillus plantarum* • *Lactobacillus paracasei*	[65, 66, 84]

VCO has a high number of medium fatty acid chains (MCFA) that make it possible to be a functional food and yield some health benefits. For instance, in cosmetics, VCO could also be used as a substance that can improve beauty that can help enhance hair growth and moisture of the skin. Moreover, a developing application of VCO is that it can be easily digestible. It has been demonstrated that its lauric acid component can show potential treatment for anti-obesity. MCFA have distinct functional and nutritional properties: antiviral, antibacterial, anti-plaque, antiprotozoal, healing, and anti-inflammatory [66]. Likewise, it was reported that VCO is said to have more beneficial effects than other oils since it can preserve most of its beneficial components [5]. A study stated VCO can decrease the total cholesterol, triglycerides, phospholipids, low-density lipoprotein, and very-low-density lipoprotein cholesterol and can increase high-density lipoprotein cholesterol in serum and tissue comparison to copra oil [67]. With these properties recognized, the further use of VCO as a multipurpose nutrient supplement can be promoted because of its nutritional and medicinal benefits.

4.2 Major pharmacological activities

4.2.1 Antiviral property

VCO is reported to be advantageous in fighting against microbes, bacteria, and viruses. Its biologically active compound with an antiviral property is flavonoids, and interest in this substance is focused on human health, specifically its antiviral, anti-allergic, antiplatelet, anti-inflammatory, antitumor, and antioxidant activities.[65] A study formally stated that the possible use of coconut oil and its derivative had been observed as efficient and safe antiviral agents against COVID-19 [68]. The coconut oil’s derivatives contain lauric acid, known for its antiviral activity; consequently, the body converts it to monoglyceride monolaurin when ingested. Its antiviral activity includes the following three crucial mechanisms: first, they can cause a disintegration of the virus envelope; second, in the replicative virus cycle, there is an inhibition of the late maturation stage, and lastly, it can prevent the binding of viral proteins onto the host cell membrane [68]. There are studies from *in vitro* studies that were proven to have an antiviral efficacy of VCO against viruses with similar morphological characteristics to SARS-CoV-2. A rapid review from the University of the Philippines Manila has thoroughly explained the mechanism of an antiviral property of VCO that includes lauric acid and monolaurin [69]. It was demonstrated that monolaurin has the capacity to disintegrate the viral cell envelope of both the RNA and DNA viruses by incorporating the fatty acids that can destabilize the lipid bilayer. The viral cell envelope helps the virus enter into the host cell, but disintegration happens when there is a decrease in infectivity. The lauric acid can help hinder the viral maturation in a process where there is a reduction of viral glycoproteins and increased incorporation in the host plasma membrane of triacylglycerol. The inhibiting activity was demonstrated *in vitro* for the Junin virus and vesicular stomatitis virus. Both are described as enveloped single-stranded RNA (ssRNA) viruses. Likewise, SARS-CoV-2 is also an enveloped ssRNA virus, and due to this, VCO has been linked to being a potential adjunctive treatment for COVID-19 patients. Humans' consumption of coconut oil is reported to disrupt the membrane lipid coating bacteria and viruses, which contains a lipid coat that encloses the DNA, thus consequently killing the pathogens without destroying the host cell. Free fatty acids can provide these antimicrobial properties such as uric acid, capric acid, and monoglycerides [70]. One study has shown that capric acid and monocaprin components have promising antiviral activity against HIV-1 infection. These components can also be seen in VCO, which may be evident that VCO can exhibit antiviral properties [71].

Table 2: Pharmacological activities found in the virgin coconut oil

Pharmacological Properties	Phytochemicals Isolated	Biomarker affected	Implications of results in the biomarker affected	Medium of assessment	References
Antiviral property	Lauric acid Monolaurin	Lipid bilayer biomarker	Disintegration of the virus membrane. Inhibits virus maturation and binding of viral proteins to the host cell.	*In vitro*	[68]
	Capric acid Monoglycerides	Viral Glycoprotein			[70]

4.2.2 Anti-inflammatory property

There has been increased attention in utilizing the VCO as an adjunctive treatment for COVID-19 because of its anti-inflammatory and antiviral properties. An *in vitro* study reported that VCO has anti-inflammatory, antioxidant, antibacterial, antifungal, and antiviral activities. Its anti-inflammatory properties reduce the Tumor Necrosis factor, a substance that causes inflammation, even Interferon- γ (IFN-γ), and Interleukins (IL-6, IL-8, and IL-5), which suppresses these inflammatory markers and protects the skin by developing skin barrier function [72]. In addition, a study has concluded that VCO can reduce epidermal hyperplasia and thickness compared to the refined coconut oil group by the expression of TNF-α and TGF-β markers as estimated by immunohistochemistry [73]. Another supporting study has reported that the VCO on RAW 264.7 cells can inhibit the expression of TNF-α, IL-6,IL-1β, iNOS, and COX-2 genes. It means that these biomarkers expressions exhibit anti-inflammatory activities [74]. Recently, one study concluded that VCO effectively lowers C-reactive protein levels among suspects and cases of COVID-19 as an adjunct therapy where meals mixed with VCO are adequate for faster recovery from COVID-19 [7]. Furthermore, a supporting study has described that VCO has effectively regulated inflammation since researchers have correlated the phytochemicals present in VCO. The antioxidant properties help scavenge free radicals that reduce inflammation [75], such as phenolic acid. VCO consists of a large amount of phenolic acids, which have antioxidant properties that help contribute to the oxidation stability associated with the nutritional and organoleptic properties [76].

Table 2: Continued

Pharmacological Properties	Phytochemicals Isolated	Biomarker affected	Implications of results in the biomarker affected	Medium of assessment	References
Anti-inflammatory property	Lauric acid Monolaurin	Tumor Necrosis factor-alpha (TNF-α) Interleukins (IL-6, IL-8, and IL-5)	Reduction of TNF- α, and Interleukins (IL-6, IL-8, AND IL05), substances that cause inflammation.	*In-vitro*	[72]
		Tumor Necrosis factor-alpha (TNF-α) Interleukins (IL-6, IL-1β) Inducible nitric oxide synthase (iNOS) COX-2 genes	The test results for TNF- α, IL-6, IL-1β, iNOS, and COX-2 genes are reported to inhibit the expression induced by lipopolysaccharide (LPS); thus, VCO has anti-inflammatory activity		[74]
		Tumor Necrosis factor-alpha (TNF-α) Transforming growth factor -β1 (TGF-β1)	VCO allows the reduction of epidermal hyperplasia and thickness in comparison to the refined coconut oil group		[73]
		C-reactive protein	Significant decline in the C-reactive protein level.		[7]

4.3 Virgin coconut oil as an adjunctive treatment for various ailments

4.3.1 Virgin coconut oil as an adjunctive treatment for various ailments

All of the phytochemicals present in the VCO are associated with why it is one of the traditional products with an extensive history of ethno pharmacological usage. There have been reports that VCO can be used as adjunctive therapy for various conditions. A study from Malaysia has concluded that the consumption of VCO during chemotherapy of patients with breast cancer can help alleviate the symptoms related to the side effects of their chemotherapy [77]. Furthermore, some studies have shown that VCO has the capability to inhibit the further elicitation of carcinogenic agents in both colon and mammary tumors in animals [78, 79]. The fact is that VCO is also abundant in medium-chain fatty acids and can be ideal for immunosuppressed individuals. That being said, it has also been studied as a potential treatment for those HIV/AIDS patients whose immune systems are critically compromised [80]. The clinical study that showed the effects of VCO on immune responses among HIV-positive patients was remarkably improved among those people who have taken VCO as their supplement [81].

VCO extracts also have an adjuvant potential on antiretroviral therapy-induced testicular toxicity. This study investigates the impact of VCO as an adjuvant to a highly active antiretroviral therapy (HAART) on the testicular ultrastructure as well as biochemical markers in the male Sprague-Dawley rats. It has been observed that VCO supplementation ameliorates the testicular morphology as it reverses the testicular ultra-structural alterations instigated by the HAART [82]. In addition to that, a study was conducted on the beneficial role of VCO as a nutritional supplement against acute methotrexate chemotherapy, which can be helpful as an adjuvant through its potential in reducing oxidative stress and the pro-inflammatory response [83].

One of the main reasons VCO is exhibited as an essential adjuvant in treating several ailments is its medium-chain fatty acids, as shown in Table 3. It has been reported that VCO contains an abundant lauric acid content of 54.06%, followed by stearic acid with only 12.06% and no presence of palmitic acid [84]. On top of that, VCO also contains myristic acid, capric acid, and caproic acid [85]. The presence of lauric acid in the VCO is responsible for its potential to prevent cardiovascular diseases because it initiates high-density lipoprotein (HDL) and decreases the total/HDL cholesterol ratio [86]. Moreover, it can be used as an alternative treatment for inflammatory acne vulgaris through deploying antimicrobial activity [87]. As for stearic acid, it provides protection against oxidative stress and can be utilized as a promoting agent for hair growth [88]. Myristic acid, on the other hand, helps type 2 diabetes patients by significantly decreasing hyperglycemia through reducing the body weight and insulin-responsive glucose levels [89]. Furthermore, capric acid inhibits the micellar growth *in vitro* of *Candida albicans* due to a resulting 0.20 of its fractionated inhibitory concentration index for 70% growth inhibition, which is considered significant [90]. It potentially impacts the stimulation of the human osteoblast (MG63) by using decanoic acid fractions from Wattakaka volubilis leaves [91]. Finally, caproic acid can be utilized to increase gene delivery without affecting biocompatibility [92]. It can also enhance the transdermal delivery of a protein such as phenylalanyl-glycine that was carried out through chemical modification by caproic acid, which will result in increasing its stability within the skin [93]. Thereby, VCO supplementation can be used as an adjunct therapy to improve the quality of life of an individual.

Table 3: Fatty acids present in virgin coconut oil are associated with its potential adjuvant to various illnesses.

Systematic Name	Common Name	Carbon Skeleton	Established therapeutic uses	References
Dodecanoic acid	Lauric acid	12:0	Lauric acid prevents the risk of cardiovascular diseases. Lauric acid helps in the treatment of inflammatory acne vulgaris.	[86, 87]
Tetradecanoic acid	Myristic acid	14:0	Myristic acid helps decrease hyperglycemia.	[89]
Octadecanoic acid	Stearic acid	18:0	Stearic acid provides protection against oxidative stress and can be used as a promoting agent for hair growth.	[88]
Decanoic acid	Capric acid	10:0	Capric acid inhibits the growth of *Candida albicans.* Capric acid has a potential impact on the stimulation of the human osteoblast (MG63).	[90, 91]
Hexanoic acid	Caproic acid	6:0	Caproic acid can be utilized to increase gene delivery and enhance the delivery of protein.	[92, 93]

5. Potential of Virgin Coconut Oil as an adjunctive treatment against COVID-19

5.1 Adverse effects of virgin coconut oil

Numerous published studies have utilized VCO as a dietary supplement for periods ranging from 4 to 6 weeks, at dosages ranging from 30 mL/day to 50 mL/day [94, 95]. The results of all investigations were positive, and no significant side effects were recorded. Though coconut oil and its derivatives have been proven to be safe and efficient immunomodulatory drugs in both people and animals, there have been few studies on the efficacy of VCO in human trials. With previous reports of its beneficial effects against numerous viral infections, this study hypothesized that VCO might be used as additional prophylaxis to avoid the progression of symptoms among suspected or probable COVID-19 patients in isolation facilities.

5.1.1 Toxicity

It has been attributed that the consumption of saturated fatty acids in the diet is likely to cause cardiovascular diseases (CVD). The composition of coconut oil contains a high amount of saturated fatty acids, and it was formerly believed that its consumption should be avoided [96]. However, population studies have shown that the consumption of dietary coconut oil did not project a higher serum cholesterol level nor an increase in the rate of mortality or morbidity in relation to CVD [97]. Coconut oil, specifically VCO, has been reported to have a positive effect on health. A study has shown that daily consumption of VCO in young, healthy adults can positively increase high-density lipoprotein cholesterol known as the "good" cholesterol and was reported to have no significant safety implications of taking the VCO daily for eight weeks [94]. The intake of these biologically active components of VCO implicates beneficial effects that can be used for the binding of prooxidant iron, scavenging of reactive nitrogen, chlorine, and oxygen species, and the inhibition of cyclooxygenases and lipoxygenases [98]. With these broad spectra of biological properties, one study revealed that VCO in the liver and kidney have a protective effect from secondary toxicity induced by cyclophosphamide and the inhibitory effect of chronic inflammatory response in murine models. Furthermore, it has been shown that VCO has been relatively used as a dietary supplement for a long time because of its nutritional value. It was observed that no toxicity had been reported [99]. In addition to that, a study that assesses the chronic safety of commercialized fermented virgin coconut oil (FVCO) in Malaysia and other Southeast Asian countries concluded that there is a good safety profile of the FVCO for long-term use safe as a therapeutic agent. It could be used as an agent for cytoprotective [100]. Furthermore, the LD50 of FVCO is determined as 5000mg/kg, considering that amount has been reported to have no lethal activity [101].

5.2 Beneficial effects of virgin coconut oil in the management of COVID-19

A study looked at the impact of VCO administered to suspect and probable COVID-19 patients in isolation facilities. Overall, the VCO group saw faster recovery from COVID-19 symptoms and a significantly more significant drop in mean C-reactive protein (CRP) levels after 28 days than the control group. These findings support the antiviral and anti-inflammatory characteristics of VCO metabolites, which have been documented in both *in vitro* and animal studies, reinforcing the therapeutic value of supplements like VCO. However, further research is needed to obtain more conclusive data on the advantages of VCO for COVID-19.

5.3 Ongoing clinical trials

In the Philippines, a randomized controlled experiment is being conducted with hospitalized covid-19 patients aged 18 and above admitted to the Philippine General Hospital.[102] Patients will be divided into two groups: those getting standard care and those receiving standard care with virgin coconut oil (15ml, three times per day for two weeks) as adjunctive therapy. Subjects will be evaluated with reference to immediate effects, including symptom recovery/resolution and hospital stay time. In Indonesia, comparative research is presently being conducted. Patients diagnosed with COVID-19 at the Central Public Hospital Dr. Sardjito, the Teaching Hospital of Universitas Gadjah Mada (UGM), and the Yogyakarta COVID-19 referral hospitals are the focus of this pilot research (RSUD Wonosari and Sleman).[103] COVID-19 participants are recruited based on inclusion and exclusion criteria and then randomly assigned to two groups. COVID-19 patients in Group I, the intervention group, received standard treatment and 15 mL of VCO twice daily for 14 days. COVID-19 participants in Group II, the control group, received standard treatment plus 15 mL of placebo twice daily for 14 days. A nasopharyngeal or oropharyngeal Polymerase Chain Reaction (PCR) swab test is used to follow both groups for four weeks.

6. Conclusion

In conclusion, despite the numerous studies of VCO tested for various pharmacological properties, no recent studies have considered the implementation of the secondary metabolites present in virgin coconut oil as an adjunct to COVID-19 treatment. However, there has been reported that the substance present in the VCO expresses antiviral and immunomodulatory activity to adjunct with antiviral drugs that could prevent host cell infection, prevent viral replication, or alleviate the severe inflammatory effects of COVID-19. VCO has antiviral and immunomodulatory properties capable of inhibiting viral growth and stimulating the immune system's defense against pathogens, respectively. Moreover, in the Philippines, *in vitro* studies have proven its ability to suppress inflammatory cytokines and lower C-reactive protein levels. Aside from the antiviral effects of flavonoids and other polyphenols present, such as uric, other phytochemical substances like tocopherol and tocotrienol are also present. These are known for being antioxidants capable of inhibiting neuronal death, inflammation, and oxidative stress. There is also phytosterol which lowers blood LDL cholesterol levels by interfering with its absorption, benefits people with type-2 diabetes. At the same time, the testing of VCO as a dietary supplement has resulted positive without side effects despite containing high amounts of saturated fats. The consumption of VCO for eight weeks daily has shown that it does not pose a risk of cardiovascular disease, especially after a study concluded that VCO is safe to use as a long-term therapeutic agent. With that, further human clinical and observational studies for the VCO are needed that will serve as confirmatory evidence in regard to its potential as adjunct therapy against COVID-19.

7. Acknowledgment

The authors would like to express the deepest and sincere gratitude to Mr. Paolo Robert Bueno of the Natural Product Laboratory, University of the Philippines, Manila, and Asst. Prof. Ruel Valerio de Grano, Ph.D., a faculty member of the Department of Biochemistry, University of Santo Tomas, for providing us invaluable guidance throughout this review.

8. References

1. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it. 2020.
2. World Health Organization. Origin of SARS-CoV-2. https://www.who.int/health-topics/coronavirus/origins-of-the-virus. 2020.
3. World Health Organization. COVID-19 situation reports 2021. Weekly Operational Update on COVID-19. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline. 30 July, 2021.
4. Lim XY, Teh BP, Tan TY. Medicinal Plants in COVID-19: Potential and Limitations. Frontiers in pharmacology 2021;12:355.
5. Marina AM, Man YC, Amin I. Virgin coconut oil: emerging functional food oil. Trends in Food Science & Technology 2009;20(10):481-7.
6. Guarte RC, Mühlbauer W, Kellert M. Drying characteristics of copra and quality of copra and coconut oil. Postharvest Biology and Technology 1996;9(3):361-72.
7. Angeles-Agdeppa I, Nacis JS, Capanzana MV, Dayrit FM, Tanda KV. Virgin coconut oil is effective in lowering C-reactive protein levels among suspect and probable cases of COVID-19. Journal of functional foods 2021, 104557.
8. Dumancas GG, Viswanath LC, de Leon AR, Ramasahayam S, Maples R, Koralege RH *et al*. Health benefits of virgin coconut oil. Vegetable Oil: Properties, Uses and Benefits; NOVA: Burleigh, Australia 2016, 161-94.
9. Lans C. Comparison of plants used for skin and stomach problems in Trinidad and Tobago with Asian ethnomedicine. Journal of Ethnobiology and Ethnomedicine 2007;3(1):1-2.
10. Lim-Sylianco CY. Anticarcinogenic effect of coconut oil. The Philippine Journal of Coconut Studies 1987;12:89-102.
11. Ogbolu DO, Oni AA, Daini OA, Oloko AP. *In vitro* antimicrobial properties of coconut oil on Candida species in Ibadan, Nigeria. Journal of medicinal food 2007;10(2):384-7.
12. Dosumu OO, Akinola OB, Akang EN. Alcohol-induced testicular oxidative stress and cholesterol homeostasis in

rats–The therapeutic potential of virgin coconut oil. Middle East Fertility Society Journal 2012;17(2):122-8.
13. Varma SR, Sivaprakasam TO, Arumugam I, Dilip N, Raghuraman M, Pavan KB *et al*. *In vitro* anti-inflammatory and skin protective properties of Virgin coconut oil. Journal of traditional and complementary medicine 2019;9(1):5-14.
14. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473-4.
15. Ducharme J. World Health Organization Declared COVID-19 a 'Pandemic.' Here's What Than Means. Time. https://time.com/5791661/who-coronavirus-pandemic-declaration/. 11, March 2020.
16. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. Jama 2020; 324(8):782-93.
17. Ganesh R, Ghosh AK, Nyman MA, Croghan IT, Grach SL, Anstine CV *et al*. PROMIS scales for assessment of the impact of post-COVID syndrome: A Cross-Sectional Study. Med Rxiv 2021.
18. Bal A, Agrawal R, Vaideeswar P, Arava S, Jain A. COVID-19: an up-to-date review–from morphology to pathogenesis. Indian Journal of Pathology and Microbiology 2020;63(3):358.
19. Holder J. 2021. Tracking Coronavirus Vaccinations Around the World. The New York Times. https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html. 19 July 2021.
20. Vennema H, Godeke GJ, Rossen JW, Voorhout WF, Horzinek MC, Opstelten DJ *et al*. Nucleocapsid-independent assembly of coronavirus-like particles by co-expression of viral envelope protein genes. The EMBO journal 1996;15(8):2020-8.
21. Mittal A, Manjunath K, Ranjan RK, Kaushik S, Kumar S, Verma V. COVID-19 pandemic: Insights into structure, function, and hACE2 receptor recognition by SARS-CoV-2. PLoS pathogens 2020;16(8):e1008762.
22. Su S, Wong G, Shi W, Liu J, Lai AC, Zhou J *et al*. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends in microbiology 2016;24(6):490-502.
23. Centers for Disease Control and Prevention. How COVID-19 Spreads, 2021. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html.
24. Azer SA. COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics. New Microbes and New Infections 2020, 100738.
25. Hagen A. COVID-19 and the Flu. American Society for Microbiology.https://asm.org/Articles/2020/July/COVID-19-and-the-Flu. 27 October, 2020.
26. Kumar M, Al Khodor S. Pathophysiology and treatment strategies for COVID-19. Journal of translational medicine 2020;18(1):1-9.
27. Hosseini ES, Kashani NR, Nikzad H, Azadbakht J, Bafrani HH, Kashani HH. The novel coronavirus Disease-2019 (COVID-19): Mechanism of action, detection and recent therapeutic strategies. Virology 2020;551:1-9.
28. Boopathi S, Poma AB, Kolandaivel P. Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. Journal of Biomolecular Structure and Dynamics 2021;39(9):3409-18.
29. Fischetti M, Hays V, Glaunsinger B. Christiansen J. A Visual Guide to the SARS-CoV-2 Coronavirus. https://www.scientificamerican.com/article/a-visual-guide-to-the-sars-cov-2-coronavirus/. 1 July, 2020.
30. Ali MJ, Hanif M, Haider MA, Ahmed MU, Sundas FN, Hirani A *et al*. Treatment options for COVID-19: A review. Frontiers in Medicine 2020;7:480.
31. Delang L, Neyts J. Medical treatment options for COVID-19. European Heart Journal: Acute Cardiovascular Care. 2020;9(3):209-14.
32. Tran J. Can Hydroxychloroquine and Chloroquine Be Used to Treat Coronavirus (COVID-19)? https://www.goodrx.com/blog/coronavirus-medicine-chloroquine-hydroxychloroquine-as-covid19-treatment/. 16 October, 2020.
33. Vora A, Arora VK, Behera D, Tripathy S. White paper on Ivermectin as a potential therapy for COVID-19. Indian journal of tuberculosis 2020;67(3):448-51.
34. Robinson J. Everything you need to know about the COVID-19 therapy trials. The Pharmaceutical Journal. https://pharmaceutical-journal.com/article/feature/everything-you-need-to-know-about-the-covid-19-therapy-trials. 2021
35. Malani AN, Sherbeck JP, Malani PN. Convalescent plasma and COVID-19. Jama 2020;324(5):524.
36. Ho KS, Narasimhan B, Difabrizio L, Rogers L, Bose S, Li L *et al*. Impact of corticosteroids in hospitalised COVID-19 patients. BMJ open respiratory research 2021;8(1):e000766.
37. Gogali A, Kyriakopoulos C, Kostikas K. Corticosteroids in Covid-19: One size does not fit all. European Respiratory Journal 2021, 57(4).
38. Jovic TH, Ali SR, Ibrahim N, Jessop ZM, Tarassoli SP, Dobbs TD *et al*. Could vitamins help in the fight against COVID-19?. Nutrients 2020;12(9):2550.
39. Dwivedi R. Vitamin C and COVID-19: A Review. News Medical Life Sciences, 2020.
40. Curley B. Vitamin D Can Help Reduce COVID-19 Risks: Here's How. Healthline. https://www.news-medical.net/news/20201023/Vitamin-C-and-COVID-19-A-Review.aspx. 2020.
41. Shakoor H, Feehan J, Al Dhaheri AS, Ali HI, Platat C, Ismail LC *et al*. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19?. Maturitas. 2021; 143:1-9.
42. Forni G, Mantovani A. COVID-19 vaccines: where we stand and challenges ahead. Cell Death & Differentiation 2021;28(2):626-39.
43. Grun G. COVID-19 vaccinations: What's the progress, 2021? https://www.dw.com/en/covid-19-vaccinations-whats-the-progress/a-55648707. 15 July, 2021.
44. Bar-Zeev N, Inglesby T. COVID-19 vaccines: early success and remaining challenges. The Lancet 2020;396(10255):868-9.
45. Faltado A, Macalalad-Josue A. Philippine COVID-19 Living Clinical Practice Guidelines: Virgin Coconut Oil 2021.https://www.psmid.org/wp-content/uploads/2021/03/ADJUNCT_VCO_Ver1_March-16-2021.pdf. 20 February, 2021.
46. Elevitch C. Species profiles for Pacific island agroforestry. Permanent Agriculture Resources series. Western Region Sustainable Agriculture Research and Education, Holualoa, Hawaii, 2006.
47. DebMandal M, Mandal S. Coconut (*Cocos nucifera* L.: Arecaceae): in health promotion and disease prevention.

Asian Pacific journal of tropical medicine 2011;4(3):241-7.
48. Broschat TK, Crane JH. The coconut palm in florida. University of Florida Cooperative Extension Service, Institute of Food and Agriculture Sciences, EDIS 2000.
49. Orwa C, Mutua A, Kindt R, Jamnadass R, Simons A. Agroforestree Database: a tree reference and selection guide. Version 4. Agroforestree Database: a tree reference and selection guide. Version 4 2009.
50. Pham LJ. Coconut (*Cocos nucifera*). In Industrial oil crops. AOCS Press, 2016, 231-242
51. Moreno ML, Kuwornu JK, Szabo S. Overview and constraints of the coconut supply chain in the Philippines. International Journal of Fruit Science 2020;20(sup2):S524-41.
52. Prades A, Salum UN, Pioch D. New era for the coconut sector. What prospects for research?. Oil Crops Supply Chain Asia 2016;23(6):1-4.
53. Castillo MB, Ani PA. The Philippine coconut industry: status, policies and strategic directions for development. Food. Fertilz. Technol. Center. (FFTC) Agri. Pol 2019.
54. Lapina G, Andal EG. ASEAN Economic Community: Opportunities and Challengers for the Crops Sector. 2017.
55. Clarete RL, Roumasset JA. An analysis of the economic policies affecting the Philippine coconut industry 1983.
56. Ranada P. Will Aquino face the marching coconut farmers? Rappler Philippines. https://r3.rappler.com/nation/74725-benigno-aquino-coconut-farmers-march-coco-levy. 2014.
57. Philippine Statistics Authority (PSA). Major Non-Food and Industrial Crops Quarterly Bulletin, January-March 2021: Coconut. https://psa.gov.ph/non-food/coconut. 2021.
58. Bawalan DD, Chapman KR. Virgin coconut oil. Production manual for micro and village scale processing. FAO regional office for Asia and the Pacific, Bangkok. Food and Agriculture Organization of the United Nations. First Published February D. 2006.
59. [59] Asanka JR, Prasangika JP, Marikkar JM, Jayasundera JM, Asanka MJ. Production of dried pulverized kernel for virgin coconut oil extraction. InSecond symposium on plantation crop research 2008; pp. 327-335.
60. [60] Kurian A, Peter KV. Commercial crops technology (Vol. 8). New India Publishing, 2007.
61. [61] Bawalan DD. Processing manual for virgin coconut oil, its products and by-products for Pacific Island Countries and Territories. Secretariat of the Pacific Community 2011.
62. Wong YC, Hartina H. Virgin coconut oil production by centrifugation method. Oriental Journal of Chemistry 2014;30(1):237-45.
63. Kabara JJ. Health oils from the tree of life (nutritional and health aspects of coconut oil). Di dalam: Sustainable Coconut Industry in the 21st Century. InProceeding of the XXXVII Cocotech Meeting/ICC 2000, 101-109.
64. Fife B. The coconut oil miracle. Avery Publishing Group, 2013.
65. Carandang EV. Health benefits of virgin coconut oil.Indian Coconut Journal-Cochin- 2008;38(9):8.
66. Ghani NA, Channip AA, Chok Hwee Hwa P, Ja'afar F, Yasin HM, Usman A. Physicochemical properties, antioxidant capacities, and metal contents of virgin coconut oil produced by wet and dry processes. Food Science & Nutrition 2018;6(5):1298-306.
67. Nevin KG, Rajamohan T. Beneficial effects of virgin coconut oil on lipid parameters and *in vitro* LDL oxidation. Clinical biochemistry 2004;37(9):830-5.
68. Dayrit FM, Newport MT. The Potential of Coconut Oil as an Effective and Safe Antiviral Agent Against the Novel Coronavirus (nCoV-2019). Ateneo de Manila University 2020.
69. Tan-Lim CS, Martinez CV. Should virgin coconut oil be used in the adjunctive treatment of COVID-19. Acta Medica Philippina 2020;54(1):66-8.
70. Bhatt KP, Pulickal AV, Agolli A, Patel MH, Thevuthasan S, Haight R *et al*. Antioxidant, Antibacterial, Antiviral and Antifungal properties of Virgin Coconut Oil (VCO). Gratis 2021, 7(1).
71. Kristmundsdóttir T, Árnadóttir SG, Bergsson G, Thormar H. Development and evaluation of microbicidal hydrogels containing monoglyceride as the active ingredient. Journal of pharmaceutical sciences 1999;88(10):1011-5.
72. Varma SR, Sivaprakasam TO, Arumugam I, Dilip N, Raghuraman M, Pavan KB *et al. In vitro* anti-inflammatory and skin protective properties of Virgin coconut oil. Journal of traditional and complementary medicine 2019;9(1):5-14.
73. Hassan SM. Anti-inflammatory and Anti-proliferative Activity of Coconut Oil against Adverse Effects of UVB on Skin of Albino Mice. Jordan Journal of Biological Sciences 2020, 13(3).
74. Amin M, Silalahi J, Harahap U, Satria D. Anti-Inflammation Activity of Virgin Coconut Oil *In-Vitro* Against Raw Cells 264.7. Asian Journal of Pharmaceutical Research and Development. 2020;8(1):55-8.
75. Chew YL. The beneficial properties of virgin coconut oil in management of atopic dermatitis. Pharmacognosy Reviews 2019;13(25):24.
76. Wallace TC. Health effects of coconut oil-A narrative review of current evidence. Journal of the american college of nutrition 2019;38(2):97-107.
77. Law KS, Azman N, Omar EA, Musa MY, Yusoff NM, Sulaiman SA *et al*. The effects of virgin coconut oil (VCO) as supplementation on quality of life (QOL) among breast cancer patients. Lipids in health and disease 2014;13(1):1-7.
78. Cohen LA, Thompson DO, Maeura Y, Choi K, Blank ME, Rose DP. Dietary fat and mammary cancer. I. Promoting effects of different dietary fats on N-nitrosomethylurea-induced rat mammary tumorigenesis. Journal of the National Cancer Institute 1986;77(1):33-42.
79. Reddy BS, Maeura Y. Tumor promotion by dietary fat in azoxymethane-induced colon carcinogenesis in female F344 rats: influence of amount and source of dietary fat. Journal of the National Cancer Institute. 1984;72(3):745-50.
80. Dayrit CS. Coconut oil in health and disease: its and monolaurin's potential as cure for HIV/AIDS. Indian Coconut Journal-Cochin- 2000;31(4):19-24.
81. Soerjodibroto W. Research Report on the Effects of Virgin Coconut Oil on Immune Responses among HIV Positive Patients in Dharmais Hospital, 2006.
82. Ogedengbe OO, Jegede AI, Onanuga IO, Offor U, Peter AI, Akang EN *et al.* Adjuvant potential of virgin coconut

oil extract on antiretroviral therapy-induced testicular toxicity: An ultrastructural study. Andrologia 2018;50(3):e12930.
83. Famurewa AC, Folawiyo AM, Enohnyaket EB, Azubuike-Osu SO, Abi I, Obaje SG *et al*. Beneficial role of virgin coconut oil supplementation against acute methotrexate chemotherapy-induced oxidative toxicity and inflammation in rats. Integrative medicine research 7(3), 257-63.
84. Suryani S, Sariani S, Earnestly F, Marganof M, Rahmawati R, Sevindrajuta S *et al*. A comparative study of virgin coconut oil, coconut oil and palm oil in terms of their active ingredients. Processes 2020;8(4):402.
85. Pramitha DA, Karta IW. Analysis of Fatty Acids in Virgin Coconut Oil Frying at Various Temperatures. JST (Jurnal Sains dan Teknologi) 202;10(1):104-11.
86. Uday Kumar D, Christopher V, Sobarani D, Nagendra Sastry Y. Lauric acid as potential natural product in the treatment of cardiovascular disease: a review. Journal of Bioanalysis and Biomedicine 2014;6(2):037-9.
87. Nakatsuji T, Kao MC, Fang JY, Zouboulis CC, Zhang L, Gallo RL *et al*. Antimicrobial property of lauric acid against Propionibacterium acnes: its therapeutic potential for inflammatory acne vulgaris. Journal of investigative dermatology 2009;129(10):2480-8.
88. Noor NM, Sheikh K, Somavarapu S, Taylor KM. Preparation and characterization of dutasteride-loaded nanostructured lipid carriers coated with stearic acid-chitosan oligomer for topical delivery. European Journal of Pharmaceutics and Biopharmaceutics 2017;117:372-84.
89. Takato T, Iwata K, Murakami C, Wada Y, Sakane F. Chronic administration of myristic acid improves hyperglycaemia in the Nagoya–Shibata–Yasuda mouse model of congenital type 2 diabetes. Diabetologia 2017;60(10):2076-83.
90. Bergsson G, Arnfinnsson J, Steingrímsson O, Thormar H. *In vitro* killing of Candida albicans by fatty acids and monoglycerides. Antimicrobial agents and chemotherapy 2001;45(11):3209-12.
91. Venugopal E, Ramadoss G, Krishnan K, Eranezhath SS, Bhattacharyya A, Rajendran S. Stimulation of human osteoblast cells (MG63) proliferation using decanoic acid and isopropyl amine fractions of Wattakaka volubilis leaves. Journal of Pharmacy and Pharmacology 2017;69(11):1578-91.
92. Layek B, Singh J. Caproic acid grafted chitosan cationic nanocomplexes for enhanced gene delivery: effect of degree of substitution. International journal of pharmaceutics 2013;447(1-2):182-91.
93. Yamamoto A, Setoh K, Murakami M, Shironoshita M, Kobayashi T, Fujimoto K *et al.* Enhanced transdermal delivery of phenylalanyl-glycine by chemical modification with various fatty acids. International journal of pharmaceutics 2003;250(1):119-28.
94. Chinwong S, Chinwong D, Mangklabruks A. Daily consumption of virgin coconut oil increases high-density lipoprotein cholesterol levels in healthy volunteers: a randomized crossover trial. Evidence-Based Complementary and Alternative Medicine 2017.
95. Khaw KT, Sharp SJ, Finikarides L, Afzal I, Lentjes M, Luben R *et al*. Randomised trial of coconut oil, olive oil or butter on blood lipids and other cardiovascular risk factors in healthy men and women. BMJ open 2018;8(3):e020167.
96. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL *et al*. Guidelines: Editor's choice: 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal 2016;37(29):2315.
97. [97] Kaunitz H, Dayrit CS. Coconut oil consumption and coronary heart disease. Philippine Journal of Coconut Studies (Philippines) 1992; 30(3):165–171.
98. Halliwell B, Rafter J, Jenner A. Health promotion by flavonoids, tocopherols, tocotrienols, and other phenols: direct or indirect effects? Antioxidant or not?. The American journal of clinical nutrition 2005;81(1):268S-76S.
99. Nair SS, Manalil JJ, Ramavarma SK, Suseela IM, Thekkepatt A, Raghavamenon AC. Virgin coconut oil supplementation ameliorates cyclophosphamide-induced systemic toxicity in mice. Human & experimental toxicology 2016;35(2):205-12.
100. Ibrahim AH, Khan MS, Al-Rawi SS, Ahamed MB, Majid AS, Al-Suede FS *et al.* Safety assessment of widely used fermented virgin coconut oil (*Cocos nucifera*) in Malaysia: Chronic toxicity studies and SAR analysis of the active components. Regulatory Toxicology and Pharmacology 2016;81:457-67.
101. Zbinden G, Flury-Roversi M. Significance of the LD 50-test for the toxicological evaluation of chemical substances. Archives of toxicology 1981;47(2):77-99.
102. ClinicalTrials.gov. (2021). Virgin Coconut Oil as Adjunctive Therapy for Hospitalized COVID-19 Patients. https://clinicaltrials.gov/ct2/show/NCT04849637. 2021.
103. ClinicalTrials.gov. Virgin Coconut Oil (VCO) as a Potential Adjuvant Therapy in COVID-19 Patients. https://clinicaltrials.gov/ct2/show/NCT04594330. 2020.