CHAPTER 14

Prescription, over-the-counter (OTC), herbal, and other treatments and preventive uses for COVID-19

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14.1 Introduction

Since November 2019, a new type of coronavirus infected patients in China.[1,2] This virus has spread rapidly to 213 countries and territories around the world causing a pandemic that at the time of writing (end of September 2020) has taken the lives of over 1 million people.[3] The COVID-19 pandemic migrated from its initial epicenter in Asia to Europe and is currently causing a tremendous burden in Latin America. This situation has exposed fragile health care systems, vulnerable socioeconomic conditions,[4] higher risk factors because of obesity and increasing rates of undernutrition,[5] lack of procurement of medical supplies,[6] and an inadequate reporting of COVID-19 cases and deaths.[7] For instance, the Ministry of Health of Peru has recognized that its health care system was fragmented before the pandemic, and the current situation has made its fragility become more evident.[8] It has been reported that Peru preferentially uses rapid serological tests (75%) to report active confirmed COVID-19 cases, which could lead to an overestimation of positive cases.[9] Latin America has not implemented public policies to control self-medication that it is currently occurring at alarming rates as speculative preventive measures against

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COVID-19 start to flourish.[10] This event has challenged many health care systems, causing the collapse of many hospitals around the globe.[7,10–13] It also impacted the global economy, leaving it vulnerable and probably prone to lose an estimated 2.4% of the GDP of the major economies.[14,15] Unemployment rates have remarkably increased, leading to a possible recession.[16] The COVID-19 pandemic was accompanied by conspiracy theories, rumors, and infodemic, aggravated because of the availability to access social media, and the development of mental health issues on the population due to the lockdown.[17–21]

Currently, with over six months of the outbreak of the pandemic, the COVID-19 crisis is expected to markedly affect people's well-being and mental health as reported in China,[22–24] Singapore,[25] Iran,[26,27] Italy,[28,29] France,[30] United Kingdom,[31] Spain,[32,33] Chile,[34] Bolivia,[35,36] Ecuador,[36–38] Brazil,[39–41] Peru,[36,42] and indigenous populations.[43] This disruption in people's work and life has been accompanied by an unprecedented infodemic of fake news.[44] This plethora of misinformation and false reports have spread faster because of social media.[44] The entire world has been affected by this infodemic, and Latin America has been no exception. However, Peru was the only country in Latin America that took a different approach by implementing prison sentences to the creators and disseminators of fake news.[17]

The infodemic has been accompanied by a surge of unproven religious and herbal treatments for COVID-19 prevention.[45] Herbal remedies or phytomedicinal self-medication use is common in developing countries[46,47] and patients often do not properly report it to their physicians.[48,49] It has been reported in a cross-sectional survey that patients do not disclose this information since they are afraid of their doctor's disagreement or negative response because most of them followed advice from a nonmedical source (family, friend, internet, or social media).[48] Other patients stated that their doctor did not ask them, while others considered that it was not necessary to inform their doctor.[48] However, possible drug-herbal interactions are discussed in various reputable pharmacopeias that detail herbal use, efficacy and safety.[50–52] Furthermore, drug-herbal interaction databases allow physicians to check possible interactions online.[53,54] This is a confounding factor since people typically self-medicate regardless of the effort of regulatory agencies to educate the population.[55] Unproven prescription drugs have been falsely promoted for COVID-19 prevention and treatment.[56] Health literacy has been defined as the individuals' capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions,[57] and to address or solve a health-related problem.[58] Latin America is a region with a low literacy rate that affects directly the drug utilization research (DUR), which encompasses the use, efficacy, and safety of medicines based on local research.[59] This is primarily caused by the existence of a very limited generation of scientific publications by local investigators.[59,60] On the available studies, data collection bias has been identified since they present methodological issues such as limited validation, small sample size, and unavailability of information and involvement of the public sector.[60] All this causes a significant impact in the clinical and regulatory decisions that impact directly the public health decision making.[61] In general, public health decisions in Latin America are adaptations of public health policies of other countries,[11] rather than an actual country-based decision justified by local research.[59] A clear example of this was the implementation of supervised walks for children and adolescents during the COVID-19 lockdown in Peru,[11] which was based on the same measure that was implemented in Spain.[62] However, this decision in Peru was implemented on May 18, 2020 when data from Spain already indicated that the number of COVID-19 cases increased in this age group,[63] but importantly occurred at the time that the Multisystem Inflammatory Syndrome in Children (MIS-C) cases kept increasing in COVID-19 children around the world.[64] This resulted in the report of the first case of concomitant MIS-C and COVID-19 in a three-year-old child in Peru, the first case in Latin America.[11]

The U.S. Food and Drug Administration (FDA) declared that there are not any approved drugs or therapeutics to treat or prevent COVID-19 yet.[65] That doesn't mean that health professionals don't know how to treat a patient with COVID-19, the management consists of symptomatic care and individualized treatment depending on the type of patient we have.[65] However, this lack of knowledge has created a pathway leading to a growth in the tendency of self-medication, self-treatment, and self-care within the society.[18,66] People put their health at risk due to peer pressure, medication availability, previous experience self-medicating, among other correlated factors.[10,13,67] For example, a person can take dietary supplements such as silver instead of receiving professional care to treat or prevent coronavirus without any sustainable evidence of the effects of those substances against the SARS-CoV-2 or the adverse effects of those products just because someone recommended it on social media or TV.[68]

This chapter intends to present the safety, efficacy, and toxicology profiles of different products that were promoted by the people during the COVID-19 pandemic promising to treat or prevent the disease, such as prescription drugs, over-the-counter (OTC) drugs, herbal products, and unproven chemicals.[13,69–72] It also shows the need to implement strategies to guide the population and health care professionals in order to take safe and effective measures to fight against this virus.[73,74] The COVID-19 pandemic has shown us that the population needs to be urgently correctly informed about the protocols, ways of prevention, unsafe medications and treatments for this disease, and what to do if a person suspects of having the disease.[75]

14.2 Health literacy and drug utilization

The Institute of Medicine[76] defined health literacy as the individuals' capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. In this sense, Sorensen et al.[77] reported that about 50% of people in eight European countries had limited knowledge of health. This could be explained because during formal education, given at elementary and high schools, health issues are not a fundamental component of the current curricula. This lack of proper health education would prevent people from taking wise decisions in health promotion for themselves and the ones surrounding them. Health literacy has a direct influence on the ability of people to filter the health information they receive. So, lack of proper health literacy is one of the reasons why people tend to receive and/or distribute news without proper verification.[78]

Digital health literacy not only requires the ability to navigate efficiently searching for trusted sources on the Internet; most importantly, it requires the ability to evaluate the quality of the information on the Internet to discern the true information from the wrong one. Digital health literacy also can be defined as the ability to search, find, understand, and evaluate health information from electronic sources and apply knowledge acquired to address or solve a health problem.[58] Likewise, to be able to communicate efficiently with health professionals through the various technologies available for making health decisions.[79] It needs to be realized that the COVID-19 global pandemic has showed us that in-person and face-to-face doctor consultations are not possible and that there are still gaps for us to understand and use the full potential of digital tools.[80] However, this will require adequate training for health professionals and users, accompanied with more funding, research, and policy changes.[80]

The progress of the countries of the American continent[81] in relation to digital health is varied. On the one hand, 61% of countries have a national digital health strategy, but several of them have yet to move from the phase of formulating digital health policies and strategies to the actual implementation of services to patients.[81] Thus, it is reported that telehealth is still in the initial stages, which could explain that the population has serious limitations to access useful information through the Internet and that they can also filter the correct information.[81] It has also reported that 52.6% have an electronic health information system but only 26.3% have legislation that supports its use in national systems, also explained by the lack of financing.[81] Even though some initial efforts for digital health ecosystem for Latin America have been implemented, large-scale or nationwide coverage of digital health interventions to support health workforce development is still rarely reported in the literature.[82–84] Because of the earlier onset of the COVID-19 pandemic in Europe, eHealth services were implemented earlier in countries such as Spain[85] and were quickly replicated in the United States.[86] As the pandemic moved toward Latin America, various countries implemented telemedicine systems with Peru,[84] Brazil,[87] and Mexico[88] taking the lead in March, while Colombia[89] implemented it in April, and Argentina[90] in May 2020. However, other countries in the region have been more resilient in this aspect, such as Uruguay, which just approved telemedicine regulations,[91] Paraguay that just launched its first official telemedicine app,[92] and Bolivia started a telemedicine pilot test to evaluate its implementation.[93]

To provide high-quality eHealth services there are certain requirements that we consider need to be followed (Table 14.1). First, it is important to empower health care professionals for them to develop sufficient digital communication skills, which starts by acknowledging that the patient might perceive eHealth by a lower quality of clinical care.[94] Second, patients need to be empowered by increasing their digital health literacy, which consists of the ability to search, find, understand, and evaluate health information

Table 14.1 Requirements to ensure the quality of eHealth programs.

Requirement 1: Empower health care professionals
Develop sufficient digital communication skills Acknowledge and circumvent the innate limitations of eHealth Provide information to patient ahead of time
Requirement 2: Empower patients
Increase their digital health literacy Adequate preparedness ahead of time

from electronic sources and apply knowledge acquired to address or solve a health problem.[58] Recently, a masterclass was published that exemplifies the actual wording to use for an eHealth consultation considering the critical components that need to be present such as greeting, introduction, courtesy, equipment check, establish remote experience, consent, signpost, preparation check, ID check, reason for call, agenda-setting, and key clinical questions.[95]

Low levels of health literacy and specifically digital health literacy are the right field to start an apparently inexhaustible spread of false information. This lack of literacy is relevant because rumors had three times more share than verified stories.[96] Furthermore, it has been reported that there is a lack of general knowledge about COVID-19 symptoms[97] and lack of information on what drugs to take.[98]

14.3 Prescription drugs

Self-medication is more common in countries where health care systems tend to be less effective because of long waiting times in health care facilities, difficulty in obtaining physicians' appointments, insufficient stock of essential medicines, delay in attention, and insufficient amount of available beds/space in health care facilities.[99] This has resulted in the self-medication of various prescription drugs that have no confirmed clinical efficacy against SARS-CoV-2,[100] which correlated with the Google trend data for web search query for the terms "hydroxychloroquine,"[101] "ivermectin,"[102] and "azithromycin"[103] when potential COVID-19 related benefits were reported in the media (Fig. 14.1). Worldwide Google trend data has been reported previously for the term "self-medication," "self-care," and "self-administration."[70]

Some of them include the antimalaria drug hydroxychloroquine,[104] the antibiotic azithromycin,[105] and the antiretrovirals lopinavir and ritonavir.[106] Because of the lack of monitoring, these drugs could cause a shortage of these drugs for patients that need them for approved conditions,[107] a direct impact in the price of these drugs,[108] and jeopardize peoples' health due to their known adverse events.[100,109]

This self-medication trend has been reported to have increased worldwide based on the number of Google searches since the pandemic started.[70] This global trend has caused a tremendous medical challenge[110,111] because the various prescription drugs currently approved for COVID-19 symptoms carry adverse drug reactions.[72] Furthermore, there is

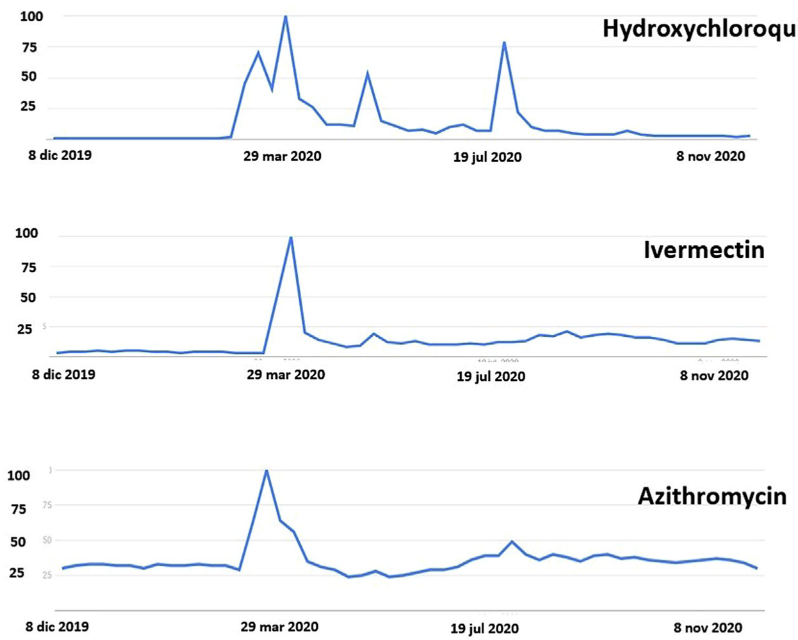

Figure 14.1 Worldwide Google trend data for web search query for the terms "hydroxychloroquine,"[101] "ivermectin,"[102] and "azithromycin."[103]

high risk of incorrect dosage, improper route of administration, longer use than intended, improper storage, risk of dependency and abuse, and increased prevalence of pathogenic resistance to drugs.[72,112] Even though self-medication intentions are common worldwide, it has only been reported in Saudi Arabia[113] and Kenya,[72] while actual statistics of prescription drug use has been reported in Peru.[13]

Regarding the consumption of the antibiotic azithromycin, an in vitro study assessed the combination of azithromycin and hydroxychloroquine showing a synergistic effect against SARS-CoV-2.[114,115] The possible antiinflammatory properties of azithromycin, which could improve the disease progression, was also reported.[114,115] However, its administration in combination therapy with hydroxychloroquine has been implicated in the elevation of the QT interval.[116] Given the limited data available to ensure the efficacy of combination therapy, the American Society for Infectious Diseases recommends that the hydroxychloroquine/chloroquine plus azithromycin combination should be limited to clinical trials.[116,117] Regarding the use of hydroxychloroquine in combination with azithromycin was publicly endorsed by President Trump, which caused self-medication causing several reports of severe poisoning in Nigeria and the United States.[108] This public endorsement triggered various in vitro and in vivo studies that reported a decrease in viral load and mitigation in the cytokine storm in critically ill patients with SARS-CoV-2.[118] Similarly, various studies reported the positive use of hydroxychloroquine and azithromycin for treatment in hospitalized COVID-19 patients.[118−121] However, the consumption of hydroxychloroquine with or without azithromycin caused an increase in cardiotoxic risk such as QT prolongation, torsades de pointes, and sudden death in hospitalized patients with COVID-19.[116,122,123] Even though the literature alerts to the possible risks with the combination of azithromycin and hydroxychloroquine, it is recommended in Peru for moderate and severe COVID-19 cases in a clinical setting since May 2020.[109,124] For mild COVID-19 patients, hydroxychloroquine is recommended at a dose of 400 mg orally every 12 h for the first day, and 200 mg orally every 12 h for 6 days.[124] In the case of moderate-to-severe COVID-19 patients, hydroxychloroquine is recommended at a dose of 200 mg orally every 8 h for 7−10 days, or hydroxychloroquine + azithromycin at a dose regimen of 200 mg orally every 8 h for 7−10 days (hydroxychloroquine) + 500 mg orally on the first day and then 250 mg every 24 h for 5 days.[124] A case report in Peru of a 13-year-old girl with encephalitis and COVID-19 serological diagnosis presented an unfavorable clinical evolution despite treatment with hydroxychloroquine, azithromycin, and corticosteroids, dying on the third day of hospitalization.[125] This published case report accompanied by the observed lack of efficacy and increased risk triggered that ivermectin, hydroxychloroquine, and azithromycin were removed from the official COVID-19 treatment in Peru.[126]

Regarding the consumption of antiretrovirals in order to prevent a viral disease such as COVID-19 it is risky because liver damage has been observed in COVID-19 patients.[127] Considering that antiretrovirals list liver damage as a common adverse effect,[128,129] it would make them inappropriate for use in COVID-19 patients. Their use is relevant for other pathologies, but a recent review has determined that there is no clear evidence of the beneficial effects of antiretrovirals in the prevention of COVID-19.[130,131] More research is still needed to determine the cost and benefit of antiretrovirals for COVID-19.

COVID-19 treatment has been a widely discussed aspect throughout 2020, with the appearance of various drugs that showed properties to control symptoms and even improve survival. As the weeks went by, these perspectives changed, leaving medicines aside, changing doses, and replacing medicines. First, it can be mentioned that there is no antiviral treatment and there is not yet a vaccine available, therefore the initial approach is based on symptom relief and oxygen therapy. In the case of patients with an oxygen saturation lower than 95%, they require high oxygen concentrations. Silent hypoxemia has been able to be detected with the use of an oximeter, which determines if the patient requires to be taken to the emergency services immediately.[132,133] Corticosteroids gained an important role, as described in the recovery trial, which shown that dexamethasone reduced deaths by a third among critical COVID-19 patients.[134] The lopinavir/ritonavir combination appeared as an alternative treatment,[135] but then studies emerged that showed superior treatments such as arbidol.[136] However, the lack of efficacy of lopinavir/ritonavir[137] and both lopinavir/ritonavir and arbidol[138] has been evidenced in COVID-19 patients. Chloroquine and hydroxychloroquine were proposed as immunomodulatory agents,[139] including their concomitant use with azithromycin.[140] The possible adverse event in the alteration of the QT interval was also reported due to concomitant use;[122] however, such adverse events were later discarded.[141] Furthermore, the use for chloroquine and hydroxychloroquine as a preventive drug for healthy and asymptomatic COVID-19 patients still needs a proper double-blind clinical trial.[142] It is important to mention that each country has adapted different pharmaceutical treatment options that are constantly updated.

14.4 Over-the-counter (OTC) drugs

OTC drugs are medicines that can be sold without a prescription directly to the consumer according to the specific regulations of each country. In the context of the COVID-19 pandemic, OTC drugs can be used as symptomatic treatment for mild COVID-19 cases without the need for the patient to go to the hospital. It is important to notice that due to the ongoing situation regarding COVID-19 pandemic, hospitals regularly are saturated. As a consequence, patients who have mild symptoms of coronavirus can be treated at home. The mild symptoms of COVID-19 include fever, dry cough, and tiredness.[143,144] It is important to note that loss of smell (anosmia) has been recognized as a prominent clinical symptom in COVID-19 patients without any other significant signs.[145,146] Since there is no available treatment for COVID-19 related anosmia[145] it is important to have a proper olfactory evaluation.[147,148] Other symptoms that are less common but still considered mild are body aches, headache,

Table 14.2 OTC drugs as COVID-19 symptomatic treatment.

Type of drug	Generic name	Symptom
Analgesic	Acetaminophen[270]	Fever, mild pain
Antiinflammatory	Ibuprofen[270]	Fever, moderate pain
	Naproxen[271]	
Cough suppressant	Dextromethorphan[272]	Cough
Antihistamines	Loratadine[273]	Nasal congestion, Sneezing
	Cetirizine[273]	
Sympathomimetic	Pseudoephedrine[274,a]	
	Phenylephrine[275]	
Opioid	Loperamide[276]	Diarrhea

[a]Pseudoephedrine is an OTC drug when combined with an antihistamine, such as loratadine or dexbrompheniramine.

sore throat, nasal congestion, and diarrhea.[143,144] We present the OTC drugs that have been recommended for mild COVID-19 symptoms. Table 14.2 shows the OTC drugs that have been used for COVID-19 symptomatic treatment.

14.4.1 Fever and body aches

In the management of fever due to COVID-19, and in general to any pathology, acetaminophen is recommended. The antipyretic effect and its safety at recommended doses make acetaminophen one of the most-used OTC drugs during the COVID-19 pandemic.[10,149] However, the increasing use of acetaminophen for managing the COVID-19 associated fever is generating concern because patients can take high doses, which can lead to acute liver injury (ALI) or acute liver failure (ALF) due to overdose.[150] Acetaminophen standard therapeutic oral dose is 0.5–1 g every 4–6 h to a maximum of 4 g/day, but more importantly it has a dose-dependent toxicity.[151] Acetaminophen can cause hepatoxicity after major overdose,[152] and severe liver damage has been observed with long-term use even at therapeutic doses in patients with alcoholic liver disease or viral infections.[153] Furthermore, it has been reported that long-term consumption of acetaminophen carries a potential risk factor for chronic renal failure,[154] cardiovascular and gastrointestinal diseases, and even mortality.[151] This is corroborated in recent studies that have reported an increase in alanine aminotransferase, aspartate aminotransferase, bilirubin, and creatinine in patients with confirmed COVID-19.[155] In addition, it has been reported that more than half of patients with ALI and ALF induced by acetaminophen have undetectable levels of acetaminophen, which is concerning.[156] Therefore, clinicians should not rule out the possibility of acetaminophen toxicity and should pay attention to patients with a history of suspected acetaminophen poisoning or associated biochemical profile.[156] This is important now with a potential significant increase in acetaminophen use due to the COVID-19 pandemic.[149]

Nonsteroidal antiinflammatory drugs (NSAIDs) play an important role in the treatment of fever and muscle aches. Ibuprofen is the most widely used OTC NSAID and has good properties for fever and pain. However, in the context of COVID-19 pandemic, it should be noted that the use of ibuprofen had a controversy due to statements in France, where it was stated that ibuprofen could worsen the clinical state in COVID-19 patients.[157,158] Nevertheless, both the World Health Organization (WHO) and the European Medicines Agency (EMA) recommended not avoiding NSAIDs when clinically indicated due to lack of scientific evidence. Recent studies suggest that there are two phases in the immune response induced by the SARS-CoV-2.[159] The first corresponds to the incubation and nonsevere stages, in which an immune response is required to eliminate the SARS-CoV-2 and prevent progression to severe stages of the disease.[159] Thus, the defense mechanism in the initial stage might be blocked by NSAIDs. The second phase corresponds to the severe stage, in which lung damage appears to be related to a cytokine storm due to an acute immune reaction.[159] It is in this second stage where the use of NSAIDs might be of more importance. In addition, the strong antipyretic efficacy of ibuprofen, which is more potent to reduce fever compared to acetaminophen, may be interfering with the benefits of a fever response.[160] Nonetheless, there is no strong evidence that can support the worsening of COVID-19 symptoms due to ibuprofen, and more research is needed such as case-control studies, cohorts, and randomized clinical trials.[161,162] Therefore, acetaminophen continues to be the first option in treating fever during the SARS-CoV-2 infection. NSAIDs are clinically recommended when the fever is high and the aches are really strong. In the case it is required to take an NSAID, although there is no significant evidence to remove ibuprofen from the list, people can opt for naproxen, which is also an OTC drug, and its effects last longer than ibuprofen. Likewise, it is important to keep in mind the presence of fever as a symptom in areas of prevalence of malaria and dengue, because it can be a factor that is confused with COVID-19 when in reality it denotes the possibility of contagion by these two diseases.[163]

14.4.2 Dry cough

In the treatment of dry cough, dextromethorphan has been widely used.[164] In the context of COVID-19, it has been reported that dextromethorphan has a pro-viral activity because it stimulated the growth of the virus in monkey epithelial cells.[165] A cellular stress coping process appears to be started by dextromethorphan, and this mechanism is also used by the SARS-CoV-2 for its replication.[165] Consequently, its use should merit caution and further study in the context of COVID-19 treatment.[165] In contrast, the TAS2R gene is believed to play an important role in host defense pathways, and has been reported that dextromethorphan is an agonist of this gene and could improve immunity especially in the treatment of dry cough.[166] However, both studies are not conclusive enough to promote or restrict the use of dextromethorphan for the management of dry cough in SARS-CoV-2 infection.

14.4.3 Nasal congestion

Despite the fact that nasal congestion is a not-so-frequent symptom during COVID-19 infection, it is a symptom that should not be ignored. There are some OTC drugs for this symptom such as antihistamines, phenylephrine, and pseudoephedrine in combination with antihistamines: pseudoephedrine and loratadine, or dexbrompheniramine and pseudoephedrine. In an experimental study, it was reported that pseudoephedrine had a protective effect in mice infected with influenza A virus because it could mitigate the cytokine storm and improved lung pathological damage.[167] However, a clinical study is still necessary to support its use in humans.

14.4.4 Diarrhea

Diarrhea is a not-so-frequent symptom in COVID-19 infection, but its management is important.[168] It has been suggested that diarrhea may be related to the use of large amounts of either antibacterial or antiviral drugs and should be considered as an adverse reaction, and consequently the first option in those cases is to suspend the use of these drugs.[169] Another proposed mechanism is that there is a direct infection of gastrointestinal cells by SARS-CoV-2, which uses ACE2 (angiotensin-converting enzyme 2) as receptor to enter the cells, and this enzyme plays an important role in regulating intestinal inflammation and diarrhea.[169] Although loperamide, an OTC drug, is widely used for milder diarrhea, there is no evidence that can support the efficacy of this drug as well as other antidiarrheal drugs. Therefore, it is suggested that adequate rehydration and electrolytes monitoring should be performed as in all patients with diarrhea.[170]

14.5 Herbals

The lack of evidence to recommend a specific treatment for COVID-19 and the absence of an available vaccine to prevent this disease, lead us to consider the supportive care and the symptomatic treatment as good strategies to deal with COVID-19. Historically, herbal medicine has been used in several epidemics of acute respiratory infectious diseases, including severe acute respiratory syndrome (SARS) and influenza.[171] This knowledge is valuable to inspire possible treatments for COVID-19.[277] In this section, we present the use of several herbal medicines, especially Traditional Chinese Medicine (TCM), that have been evaluated in randomized controlled trials (RCT) and some other herbal compounds with an antiviral effect that have evaluated in preclinical studies.

14.5.1 Prevention

Several studies showed good experience using TCM for the prevention of SARS cases during the outbreak of 2003.[172] Due to structural and genetic similarities between SARS-CoV and SARS-CoV-2, TCM is proving also to prevent COVID-19 cases currently. A prospective randomized study in 22,065 subjects, evaluated the use of *Huoxiang Zhengqi* oral liquid and *Jinhao Jiere* granules to prevent COVID-19; however, no suspected or confirmed COVID-19 case occurred in the control and intervention group, which did not make it possible to assess their effectiveness against COVID-19.[173] There is a controversial study in Israel that reported that people with vitamin D deficiency in plasma was associated with a higher risk of COVID-19 infection,[174] whereas other studies in the United Kingdom did not find any association between the Vitamin D plasma level and the risk of COVID-19 infection[175] or severe COVID-19.[176]

14.5.2 Treatment

There is a large number of studies, and they were summarized in two systematic reviews and meta-analysis of RCTs by Xiong et al.[177] and Wang et al.[178] that compared the use of TCM plus standard care, in comparison with standard care only, in COVID-19 patients. For these studies, the standard care included antiviral drugs, antibiotics, corticosteroids, supportive oxygen, and others, whereas TCM included more than a 100 herbals. The top five most common were licorice root, baical skullcap root, pinellia rhizome, forsythia fruit, and bitter apricot seed. Potential positive benefits have been published, however, most of them have a high risk of bias and small sample size,[177,178] which do not allow us to truly recommend its use in COVID-19 patients.

14.5.2.1 Clinical improvement

It has been reported that TCM reduce the length of hospitalization in terms of clinical symptoms score showing positive results for COVID-19 symptom improvement in patients that received TCM compared to standard care.[177,178] Wang et al.[178] included studies with different scales to assess this outcome and it may explain the high heterogeneity ($I^2 = 94\%$). However, in the Xiong et al.[177] study this outcome was measured in just two studies not generating heterogeneity, and the pooled result maintained its direction and significance. It was also observed that TCM reduced the number of cases of cough and fatigue and the duration of fever and fatigue in COVID-19 patients.[177] In terms of biomarkers, the C-reactive protein was reported to be significantly lower in the intervention group in the pooled result in both meta-analyses.[177,178] However, no significant differences were found in white cell count and lymphocytes between the intervention and the control group. According to CT findings, COVID-19 patients who were treated with TCM plus standard care had significantly better improvement than the control group, in both meta-analyses.[177,178]

14.5.2.2 Mortality and adverse events

The overall result from the meta-analysis showed no significant differences in the number of deaths. No severe or moderate adverse effects were reported in any of the systematic reviews; no significant differences were found between intervention and control group. The most common type of adverse event was gastrointestinal, but the recovery was rapid.[177,178]

14.5.2.3 TCM in a guidelines of treatment for COVID-19

The sixth edition of the Guidelines of Diagnosis and Treatment for COVID-19 for China[179] recommended the use of TCM according to the stage of the disease. For the patients in the medical observation period with fatigue with gastrointestinal discomfort: *Huo Xiang Zheng Qi Shui*, and for fatigue with fever: *Lian Hua Qing Wen capsule*, *Shu Feng Jie Du capsule*, and *Jin Hua Qing Gan granule*. For confirmed COVID-19 case with mild disease they recommend *Qing Fei Pai Du Tang*. For severe COVID-19 they recommended *Xi Yan Ping injection*, *Xue Bi Jing injection*, Re *Du Ning injection,* Tan *Re Qing injection*, *Xing Nao Jing injection*, and *Qing Fei Pai Du Tang*. For COVID-19 patients who required intense care they recommended *Shen Fu injection*, *Sheng Mai injection*, *Shen Mai injection*, *Su He Xiang pill*, and *An Gong Niu Huang pill*.

In July 2020, the number of the registered clinical trials for COVID-19 were 75, of them 26 aimed to evaluate TCM and only 19 aim to evaluate the combinations of TCM and Western medicine.[180] Unfortunately, most of them have several limitations since the design protocol that may not permit to validate their results and conclusions.

14.5.3 Potential candidates for clinical trials

Several herbal isolated compounds have been proved in preclinical studies as a potential inhibitor for SARS-CoV-2. Several phytochemicals were assessed in silico using molecular docking that showed that oleanolic acid extracted from *Allium cepa* was a superior inhibitor for SARS-CoV-2 than remdesivir, whereas *Moringa olifera* did not show any antiviral effect.[181] However, these findings need to be assessed in in vitro and in vivo future studies. Regarding TCM, baicalin and baicalein extracted from *Shuanghuanglian* were described as potent antiviral agents against SARS-CoV-2 in an in vitro study.[182]

14.5.4 Dietary supplements

14.5.4.1 Zinc

Zinc has proved its effectiveness against common flu and immunological prevention among some risk patients like older adults.[183] For instance, high oral dose of zinc salts has been reported to improve clinical indicators such as oxygen saturation and fever in COVID-19 adult patients.[183] However, this study was performed only in four (4) patients and further investigation in a larger group of patients is necessary. Currently, four registered clinical trials are being performed to evaluate the comparative effectiveness of zinc supplements against vitamin C and usual care for the treatment of mild-to-moderate symptoms of SARS-CoV-2 community acquired.[184]

14.5.4.2 Vitamin C

For many years, the administration of ascorbic acid has been prescribed to enhance the immune system in patients who are susceptible to viral diseases such as common flu.[185] Thus, a study performed in mice showed that vitamin C (ascorbic acid) combined with red ginseng juice enhanced T-cell immune response and stimulated NK cells.[186] In the same study, the interruption of the influenza A viral lytic cycle was observed accompanied with an improved toleration to lung inflammation.[186] A systematic review of ongoing randomized clinical trials related to the use of vitamin C in

COVID-19 patients identified that a high dose of vitamin C improved biomarker levels such as ferritin and D-dimer, and caused a trend to decrease oxygen requirement after the infusion of vitamin C.[187] Similarly, a case report illustrated the clinical improvement of a patient after five days of infusion with vitamin C.[187] Thus, vitamin C has been proposed a prophylactic and adjunctive medical treatment for COVID-19.[188]

14.5.4.3 Omega-3

A Cochrane meta-analysis of 10 studies examined the effects of omega-3 fatty acids, γ-linolenic acid and antioxidants in acute respiratory distress syndrome (ARDS) patients.[189] Quality of evidence was identified exhibiting no benefits in mortality and uncertain effects in reducing intensive care unit (ICU) length of stay, ventilator days, or oxygenation.[189]

14.6 Unproven chemicals

The COVID-19 pandemic has caused the disruption in people's work and life, which has been accompanied by an unprecedented infodemic of fake news.[44] This plethora of misinformation and false reports have spread faster because of social media.[44] The infodemic has been matched with a low health literacy condition across the world. Health literacy has been defined as the individuals' capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions,[57] and to address or solve a health-related problem.[58] All this has caused a surge and revamping of unproven chemicals that has been promoted as preventives and even miracle cures for COVID-19.[45] In this section we present the reported efficacy, safety, and toxicology profile of some of these speculative preventive and treatment options against COVID-19 such as Miracle Mineral Solution (MMS),[190] chlorine dioxide solution (CDS),[191] colloidal silver,[192] and hydrogen peroxide,[193] which is summarized in Table 14.3.

14.6.1 Chlorine dioxide solution (CDS) and Miracle Mineral Solution (MMS)

CDS is a chemical that has previously been portrayed as a miracle cure for multiple diseases,[226] and has been revamped in the current pandemic as an unproven cure and preventive for COVID-19.[191] Multiple health and sanitary regulatory agencies around the world do not support nor recommend the prophylactic use of chlorine dioxide and its chemical predecessor Miracle Mineral Solution (MMS) in humans.[194] The CDS defenders cite the unpublished research work of its most representative promoter Andreas Ludwig Kalcker and his pending patent applications.[227–229] They also cite

Table 14.3 Summary of the efficacy, safety, and toxicology profile of unproven chemicals used as speculative preventive and treatment options against COVID-19.

Unproven chemical	Efficacy	Safety	Toxicology profile	References
Chlorine dioxide solution (CDS)	NEE[a]	NEE[a]	Nausea, vomiting, diarrhea, severe dehydration, anuria, unconsciousness, cyanosis and chocolate brown serum.	194–203
Miracle Mineral solution (MMS)	NEE[a]	NEE[a]	Nausea, vomiting, diarrhea, severe dehydration, fever, chills or rigors, tachycardia, and dry cough	194–203
Colloidal silver	NEE[a]	NEE[a]	Argyria or jaundice, dehydration, fever, confusion, hypotension, hypoxia, lethargy, slurred speech, organ damage, profound disfiguration, hypochloremia, hyponatremia, cell apoptosis or necrosis, oxidative stress, and cholelithiasis	204–221
Hydrogen peroxide	NEE[a]	Not safe	Vomiting, gastric injury, skin burning or mechanical pressure injury, oxygen embolism, unconsciousness, and respiratory paralysis	193,222–225

[a]NEE = Not Enough Evidence.

the unpublished online testimonies, misinterpreted research animal and human studies, and its presumed safety based on its use in water treatment and blood transfusion bags.[190,230] CDS supporters have drafted 25 protocols to use CDS (alone or in combination with dimethyl sulfoxide [DMSO]) via the oral, intravenous, rectal, vaginal, topical, and ocular route in adults and children.[230] These *protocols* do not have efficacy nor safety data nor regulatory agency approval anywhere in the world. The FDA first warned consumers about the dangers of MMS and CDS in 2010,[194] however, people are still ingesting it, and their numbers appear on the rise, especially since the COVID-19 pandemic.

14.6.1.1 Efficacy

The promoters of CDS and MMS are making false and dangerous claims by presenting them as a remedy for autism, cancer, HIV/AIDS, hepatitis, flu, and recently, COVID-19.[194,231] Their promoters declare that vomiting and diarrhea are evidence that CDS or MMS is working; however, this lacks any scientific evidence that supports its safety or efficacy.[194,197,199]

14.6.1.2 Toxicology profile

This chemical can cause nausea, vomiting, diarrhea, and symptoms of severe dehydration.[195–197] There is a case report of life-threatening complications from poisoning with sodium chlorite, where a 55-year-old man arrived to the ICU in a cyanotic state with lowered consciousness displaying anuria and chocolate brown serum.[200] The patient required renal replacement therapy, treatment with methylene blue, and red blood cells transfusion.[200] Another case report indicated that a 41-year-old woman developed Kikuchi-Fujimoto disease (KFD)[201] after consuming MMS, which resulted in fever spiked to 40°C, chills, tachycardia, rigors, and dry cough.[202] She recovered after 16 days of treatment for her symptoms and continuous follow-up.[202] The use of these unproven chemicals is dangerous, and extreme caution needs to be implemented.[203]

14.6.2 Colloidal silver

Colloidal silver is a substance that consists of silver nanoparticles suspended on a liquid in very low quantities, similar as in homeopathy.[192] In humans, silver is absorbed through inhalation, parenteral route, ingestion, or topically, and most of it is metabolized by binding with other proteins in the liver and kidneys.[232]

14.6.2.1 Efficacy

Researchers have found that colloidal silver nanoparticles have antifungal, antibacterial, and antiviral activity.[205–207,232] Negatively charged silver nanoparticles showed a significantly higher antibacterial activity than regular colloidal silver.[208] It has been reported that silver can inhibit the replication of the following viruses: HIV-1, Hepatitis B virus, Tacaribe virus, recombinant respiratory syncytial virus, Influenza A/H1N1 virus, monkey pox virus, herpes simplex virus-1, human parainfluenza virus, vaccinia virus, murine norovirus-1,[209,210] and H3N2 Influenza virus.[211] However, further research must be performed to assess the effect of colloidal silver against SARS-CoV-2.

Another study done with the transmissible gastroenteritis virus (TGEV, a type of coronavirus) has shown that pure silver nanoparticles and silver nanowires do have inhibitory action against TGEV coronavirus, but colloidal silver does not.[212] Colloidal silver as people consumed today (orally and topically), might not help to prevent or treat COVID-19, but inhaling 3–7 nm colloidal silver particles could have an effect against bacteria and viruses (such as the SARS-CoV-2) without the risk of developing drug resistance in the lungs.[213,214] It has been reported that silver could help in the treatment of different types of cancer, such as breast cancer, leukemia, lung carcinoma, and skin carcinoma, among others.[209] However, the results are inconclusive and more studies are necessary.

14.6.2.2 Safety

Contradictory literature is found about the use of silver and its interaction within the organism. Some researchers say that silver nanoparticles are safe to use, and that is why many products used today contain silver, such as creams for burned skin and dressings for open wounds.[215,233] Other researchers discourage the use of this substance, claiming that it can cause leukocytoclastic vasculitis, argyria, neurological symptoms, and problems in different organs after long-term consumption.[216,217]

14.6.2.3 Toxicological profile

In high concentrations or long-term ingestion, silver can cause argyria, an irreversible brown-black pigmentation on tissues caused by the accumulation of silver granules, which seems to not be harmful to the patient.[204,233] Other scientists reference silver's toxicity because in high quantity or over a prolonged time, it can cause neurological problems (confusion), hypochloremia, hyponatremia, profound disfiguration, damage to mitochondria reducing the cellular ATP content, and increases the generation of reactive oxygen species (hydrogen peroxide and superoxide production) leading to oxidative stress.[209,218–220] Furthermore, it can cause damage in the DNA-promoting apoptosis, recruitment of E-cadherin to the junction between cultured keratinocytes, irregularities in the cycle of mitosis or changes in the chromosomal structure, changes in the structure of the cellular cytoskeleton and increase in cell migration in cultured keratinocytes.[209,218–220] This could cause hypotension, jaundice, obscure fingers, dry mucous membranes, cholelithiasis, lethargy, fever, hypoxia, slurred speech, and accumulation of silver in different organs (liver, spleen, lungs, colon, and kidneys) that can lead to long-term damage.[209,218–220] Another study reported that silver nanoparticles are four times less toxic than silver ions, but they still cause an increase in the levels of apoptosis and necrosis in THP-1 monocytic cells as the concentration and time increase.[234] It also needs to be mentioned that silver nitrate causes damage, inhibits metabolic activity, and reduces or suppresses the proliferation activity in keratinocytes, diminishes fibroblasts activity, and attacks feeder cells of keratinocytes.[221]

14.6.2.4 Legal issues

During the COVID-19 pandemic, many businesses, politicians, and anti-vaccination groups have taken advantage of the misinformation and desperation of the people to take unacceptable measures, such as selling unauthorized products like colloidal silver to treat and prevent coronavirus.[69,235] Due to this, the FDA's Office of Criminal Investigators and the Department of Justice of the United States of America have taken legal actions against companies, such as *My Doctor Suggests LLC* and *GP Silver LLC,* that were accused of promoting and selling silver-based products to cure and prevent COVID-19.[236–238]

14.6.3 Hydrogen peroxide

Intentional ingestion of high concentration hydrogen peroxide for health purposes has gained popularity in certain patient populations, purported benefits are due to the increased oxygen released into the bloodstream.[193] Hydrogen peroxide is also known as oxydol or dihydrogen dioxide, which is a chemical that appears as a colorless liquid, used in the production of inorganic and organic chemicals.[239,240] It is also used in a wide range of cleaning and personal care products, including surgical disinfectant, toothpaste and mouthwashes, bathroom cleaners and laundry stain removers, hair dyes, and bleaches.[239,240] Hydrogen peroxide can also be found in OTC first-aid antiseptics; it is used as a bleaching agent in some food products, and it has other consumer and industrial uses as well including water treatment.[239,240] Hydrogen peroxide is available in dilute form (3%–10%) for household use and OTC and in concentrated form (greater than 30%) for industrial use.[222]

Hydrogen peroxide injected into the bloodstream is considered an alternative treatment that claims to cure cancer, called hyperoxygenation therapy. This theory is based on the erroneous concept that cancer is caused by oxygen deficiency and can be cured by exposing cancer cells to more oxygen than they can tolerate. There is no evidence that this treatment can cure any serious disease, and it has been reported to be potentially harmful.[223] At the same time, there is also no evidence that gargling diluted hydrogen peroxide eliminates SARS-CoV-2, which was another theory that hydrogen peroxide can help prevent COVID-19.[224]

14.6.3.1 Efficacy

The SARS-CoV-2 can be persistent on inanimate surfaces, and this is why there is a list of biocidal chemicals such as hydrogen peroxide. This product is known to clean areas that might be contaminated with virus such as SARS-CoV-2. The efficacy of this chemical with a concentration of 0.5% is effective within 1 min.[241] However, its use is limited to inanimate surfaces, while no evidence exists for oral ingestion.

14.6.3.2 Safety

The growing naturopathic health industry has promoted the use of hydrogen peroxide in treating a wide variety of medical conditions. Ingestion of hydrogen peroxide can cause poisoning and results in morbidity through three main mechanisms: direct caustic injury, oxygen gas formation, and lipid peroxidation. Severe toxicity has resulted from the use of hydrogen peroxide solutions to irrigate wounds within closed body cavities or under pressure as oxygen gas has resulted in embolism.[193,225]

14.6.3.3 Toxicological profile

Hydrogen peroxide ingestion, inhalation, or contact with skin and eyes can be toxic. The severity of the effect depends on the concentration. Low concentrations can cause vomiting, mild gastrointestinal irritation, and gastric distension. Higher concentrations (>35%) can burn the exposed skin entering the adjacent tissues and blood vessels, consequently causing mechanical pressure injury and causing gastrointestinal erosion, oxygen embolism, and loss of consciousness followed by respiratory paralysis.[193,222,224]

14.7 Medication therapy management

In the health care system, a series of steps are established to ensure that patients who attend health care centers can achieve medical attention to their ailments. So, when it comes to chronic diseases, patients manage to get medical diagnosis and receive a prescription. However, the medical literature shows different results in relation to the control of diseases, which is directly related to the level of health literacy of patients.[242] In this way, it has been possible to recognize problems in adherence to drug treatment, especially in chronic diseases as diabetes,[243] tuberculosis,[244] glaucoma,[245] hypertension,[246] and others. Nonadherence is a drug-related problem.

14.7.1 Drug-related problem

Pharmaceutical Care Network Europe (PCNE) stablished the definition for drug-related problem (DRP) as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.[247] DRPs have been reported in different types of patients such as ischemic stroke,[248] epilepsy,[249] rheumatoid arthritis,[250] and other illnesses.

14.7.2 Medication therapy management/pharmaceutical care

To identify, solve, and prevent DRPs, a clear methodology is required, and for this there is the medication therapy management, also known as pharmaceutical care, which seeks to contribute to achieving therapeutic goals as in the case of patients with diabetes,[251–253] hypertension,[254,255] and other diseases. However, some barriers to provide pharmaceutical care have been detected.[256,257] It seeks to reduce the discrepancies between what is indicated by the doctor and the drugs that are finally used by the patient. In this way, it is possible to reduce DRPs, which achieves three specific impacts: reduction of workload, reduction of morbidity and mortality, and reduction of (re)hospitalizations (Fig. 14.2).[278,279]

14.7.3 Pharmaceutical care during the COVID-19 pandemic

COVID-19 is an infectious disease of pandemic proportions, with more than 34 million cases and over 1 million deaths reported worldwide (at the time of writing).[3] The current pandemic has generated many problems with the use of drugs for prevention and treatment, influenced by fake news[17] and other aspects. During COVID-19, people have needed to receive pharmaceutical care and it has been shown that pharmacists have been able to provide different services to patients. The care of patients with COVID-19 within hospital settings presented different limitations that has

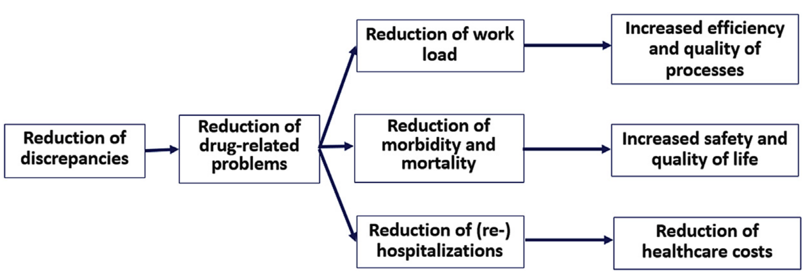

Figure 14.2 Impact of reduction of discrepancies in the use of medication.

generated negative impact in the mental health and job satisfaction of health care professionals.[12,26,35,37,258] Despite this, it has been possible to report clinical interventions to optimize the use of medications and avoid self-medication. There is a need for health professionals to guide patients and their families to take the necessary actions to prevent further infections, especially the most vulnerable.[9,11,259–261] Thus, Cadogan and Hughes[262] recognized that pharmaceutical care can contribute to the following actions:

1. Provide objective and reliable information on the disease and associated symptoms.
2. Educate the public about infection control and preventive measures to reduce transmission (e.g., hand hygiene, social distancing, and self-isolation).
3. Implement infection control measures (e.g., cleaning and disinfection of the pharmacy environment, limiting public access to the pharmacy).
4. Maintain continuity of pharmacy services, including supplies of essential medications and other products (e.g., hand sanitizers, protective masks).
5. Facilitate continued supply of OTC and prescription medications to patients (including emergency supply of repeat medications where necessary).

Likewise, Li et al.[263] were able to recognize innovative strategies to deal with COVID-19 such as establish evidence-based drug evaluation and guidelines; remote inpatient order review and dispensing tele-pharmaceutical care, telehealth counseling, and patient education; and multimedia health education. At the hospital level, Song et al.[264] has also evidenced the contribution in medical rounds of pharmacists to optimize pharmacotherapy. Many community pharmacies have been on the frontline of health service to fight against COVID-19, dispensing products, and providing counseling about drugs to patients,[265] and fighting against misinformation.[266] Specifically, there is evidence from Germany that shows that pharmaceutical care in the pharmacy, telephone, and video call was provided from community pharmacies with 44.2% of pharmacies that conducted medication reviews during the COVID-19 epidemic. The contribution from the rural pharmacy in actions against COVID-19 has even been described.[267] In China expert teams were created to focus on issues related to pharmaceuticals, pharmacokinetics, and pharmacotherapy, as well as treatment alternatives due to drug shortages.[268] Finally, it has been reported that telepharmacy services have continued to guide patients.[269]

Fig. 14.3 shows that medication therapy management/pharmaceutical care must consider the different kind of information that the patients

Figure 14.3 Information sources for health decision making.

receive to work closely with them to make good health decisions to prevent adverse events and the patient can reach the therapeutic goals during COVID-19 care.

Health care systems need to empower health professionals who have direct access to the population as in the case of community pharmacists, whom the population had available to make consultations during the COVID-19 pandemic. Community pharmacists have served as source of information for the general public[280,281] to clearly understand the messages from the authorities and prescribers, to avoid self-medication and to report adverse reactions by the use of prescription and OTC drugs, herbals, and unproven chemicals for the treatment of COVID-19.

14.8 Conclusion

COVID-19 is a new disease and we are still understanding its pathophysiology and symptomatology, and are in the process of producing an effective and safe vaccine and specific treatments. Currently, various prescription and OTC drugs, herbal products, and unproven chemicals have been used in an effort to manage the COVID-19-related symptoms. The efficacy, safety, and toxicology of these has been presented, and caution needs to be taken with all of them. Medication therapy management or pharmaceutical care is critical as well as consultation with community pharmacists. The sense of urgency and desperation against a pandemic is evident, but the caution against the preventive and COVID-19-related symptom treatment is warranted. Future studies and therapeutic strategies will continue to be produced in order to counter a pandemic that has affected so many people and lives across the globe.

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