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The potential of Ethiopian medicinal plants to treat emergent viral diseases

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REVIEW

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The potential of Ethiopian medicinal plants to treat emergent viral diseases

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Abstract

Ethiopians have deep-rooted traditions of using plants to treat ailments affecting humans and domesticated animals. Approximately 80% of the population continues to rely on traditional medicine, including for the prevention and treatment of viral diseases. Many antiviral plants are available to and widely used by communities in areas where access to conventional healthcare systems is limited. In some cases, pharmacological studies also confirm the potent antiviral properties of Ethiopian plants. Building on traditional knowledge of medicinal plants and testing their antiviral properties may help to expand options to address the global pandemic of COVID-19 including its recently isolated virulent variants and prepare for similar outbreaks in the future. Here, we provide an ethnobotanical and pharmacological inventory of Ethiopian medicinal plants that might contribute to the prevention and treatment of viral diseases. We identified 387 species, about 6% of Ethiopia's known flora, for which records of use by local communities and traditional herbalists have been documented for the treatment of viral diseases. We provide a framework for further investigation and development of this vital resource much anticipated to help combat emergent viral diseases along with existing ones in Ethiopia and elsewhere.

KEYWORDS

antiviral plants, Ethiopia, ethnobotany, ethnopharmacology, traditional herbal medicine

1 | INTRODUCTION

Traditional medicine is the sum of knowledge, skills, and practices based on the theories and experiences of different cultures used to prevent, diagnose, improve, and treat physical and mental illnesses (World Health Organization, 2013, 2020a, 2020b). Traditional medical practices are unique to different regions and cultures based on plants, animals, fungi, and other resources available within local ecosystems (Ekor, 2014). A growing number of people in Africa, Asia, and Latin America use traditional medicine to meet some part of their primary healthcare needs (Oyebode et al., 2016; So et al., 2018). In developing countries, up to 80% of people rely on traditional medicine for their primary healthcare (Ekor, 2014; Hamilton, 2004).

Globally, up to 50,000 plant species have been used as sources of traditional medicine (Chen et al., 2016). Research results suggest that the use of medicinal plants is increasing worldwide (Ekor, 2014; Jamshidi-Kia et al., 2018). Medicinal plants are distributed across all six inhabited continents, but the vast majority originate in tropical countries (Chen et al., 2016). Demand for medicinal plant products is also increasing in industrialized countries, as consumers prefer natural products for therapeutic uses as well as dietary supplements (Ekor, 2014; WHO, 2004). The global market for medicinal herbs is expected to grow fivefold in the next 10 years due to a high preference for natural and organic over conventional pharmaceutical products (Bareetseng, 2022; Nirmal et al., 2013; Te, 2013). The COVID-19 pandemic has only added to this trend (Vandebroek et al., 2020).

Traditionally used plants have made major contributions to allopathic "Western" medicine by providing active ingredients for drug discovery and synthesis (Pan et al., 2013; Süntar, 2020; Yuan et al., 2016). Many important drugs are still extracted directly from plants, while others are produced through the transformation of extractions. Still others are synthesized from inorganic materials but are modeled on compounds found in plants used in traditional medicine (Dias et al., 2012; Hamilton, 2004; Katiyar et al., 2012). Traditional herbal medicines from diverse geographical locations and various habitats are considered potential sources of new drugs for the treatment of viral infections, including those caused by severe acute respiratory syndrome-related coronavirus (SARS-CoV) (Islam et al., 2020). For example, traditional Chinese herbal medicine, both alone and in combination with Western medicine, significantly improved symptoms of SARS (Li et al., 2005) by decreasing body temperature, cough and breathing difficulties, shortening corticosteroids treatment, improving absorption of pulmonary infiltration, and restoring health and upscaling the quality of life (Liu et al., 2012). Several antiviral plant extract tests showed effectiveness against SARS (Lelešius et al., 2019). Antiviral plants are plants reported in traditional or modern medicine to have activities when used to treat ailments caused by viruses/viral agents. An aqueous extract called TSL-1 from the tender leaves of *Toona sinensis* (Meliaceae) was effective against SARS-CoV in vitro (You et al., 2013). The extract was subsequently tested against the pandemic influenza A virus (2009H1N1) where it inhibited the viral activity by suppressing viral attachment onto the A549 cells. Moreover, in comparison with the H1N1 drug amantadine, the TSL-1 treatment was associated with a better effect on the downregulation of adhesion molecules and chemokinesis (You et al., 2013, 2018). Another study on *Loranthus ramulosus* (Loranthaceae) was even more effective against SARS-CoV in Vero E6 cells, this time via anti-RNA replication pathways (Vlietinck et al., 1995). Similarly, compound extracts from *Ungernia trisphaera* (Amaryllidaceae), *Artemisia annua* (Asteraceae), *Pyrrosia lingua* (Polypodiaceae), and *Lindera aggregata* (Lauraceae) have shown antiviral activity against SARS-CoV strain BJ001 in Vero cell-based CPE/MTS screening (Li et al., 2005). The addition of active compounds significantly blocked viral infection or replication and kept cells in a viable state (Mm et al., 2011). *Pelargonium sidoides* (Geraniaceae), a species native to South Africa, was also reported for its antiviral activity against rhinovirus, seasonal influenza A virus, human coronavirus, respiratory syncytial virus (RSV), coxsackie, and parainfluenza (Ho et al., 1996; Li et al., 2005; Roth et al., 2019).

Ethiopia is a rugged, mountainous country with elevations ranging from 125 m below sea level to 4533 m above sea level (Ethiopian Biodiversity Institute, 2022). Due to its environmental heterogeneity as well as its cultural diversity, Ethiopia is one of the richest countries in the Horn of Africa in terms of plant diversity (Asefa et al., 2020; Friis et al., 2005), with nearly 6000 vascular plant species, of which approximately 10% are endemic (Kelbessa & Demissew, 2014). Ethiopians have learned to use plants for a wide range of medicinal purposes as shown in ancient pharmacopeias and research (Fullas, 2001). More than 887 plant species have been used in Ethiopia's traditional medicine to treat various ailments (Tanto et al., 2003). There are few records of the use of traditional medicine in Ethiopia before the 16th century (Gaym, 2006; Pankhurst, 1990). However, the most detailed account of the uses of medicinal plants, including the diseases they are known to treat, is found in the book titled *Etse Debdabe* (literally, the "plant letter") (Abate, 1989), which contains medicinal knowledge from the Ethiopian Orthodox clergy that had passed by word of mouth from generation to generation and until it was finally documented in the 20th century. Early written accounts of useful plants including medicines were documented by European travelers, including James Bruce (1769–1771), Henry Salt (1805, 1809–1810), and Eduard Rüppell (1768–1833) (Friis, 2013; Tadesse, 1994).

Approximately 80% of the Ethiopian population relies on traditional medicine, which is heavily dominated by the use of herbal medicines, for their primary healthcare (Birhan et al., 2011; Wassie et al., 2015). Even in urban areas like Addis Ababa, traditional medical services are more readily available and therefore more widely used than allopathic medicine (Abebe & Ayehu, 1993; Birhan et al., 2011; Birhanu et al., 2015). Since 2020, the country's medical supply chain has barely kept up with the enormous demand for drugs to treat COVID-19-associated medical complications, such as pneumonia and acute respiratory distress syndrome. Medicinal plants, on the other hand, have been traditionally used for centuries to treat viral respiratory symptoms in Ethiopia.

Ethnobotanists and others have conducted numerous surveys of medicinal plants, each focusing on a particular cultural group or subset of plants used for the treatment of certain kinds of ailments (some examples include Abate, 1989; Birhanu et al., 2015; Giday et al., 2003, 2009; Hunde et al., 2006; Lulekal et al., 2008, 2014; Maroyi, 2014; Molla et al., 2014; Yineger et al., 2008). However, these findings are scattered across various publications, dissertations, and other reports and require consolidation and systematic analyses. We believe it is necessary to develop and scale up the use of medicinal plants to combat existing and emergent viral diseases within the country and elsewhere. Therefore, the aims of this article are (1) to review the history of viral pandemics in Ethiopia and the experiences that have contributed to the identification of plants with antiviral properties; (2) to compile a list of plants that have been used to treat viral diseases in Ethiopia from the ethnobotanical literature; and (3) to review pharmacological studies conducted on Ethiopian antiviral plants and recommend potential plant species to be tested against the SARS-COV2 virus.

2 | PREVIOUS VIRAL EPIDEMICS IN ETHIOPIA

Ethiopia has experienced numerous epidemics, including many that were likely caused by viral diseases such as smallpox, influenza (flu), and rabies (Pankhurst, 1965, 1970, 1977). The first two epidemics on record, documented in the *Metshafe Senkesar* (Ethiopian Synaxarium), came in the wake of horrible periodic famines (Pankhurst, 1990). The first of these appeared in Ethiopia on the 23rd of *Teqemt/Tiqemt* (October), assumed to have happened sometime between 831 and 849 AD. Three centuries later, a second epidemic occurred on the 10th of *Miyazya* (April), sometime during the patriarchy of Saint Gabriel between 1131 and 1145 AD (Pankhurst, 1990). Sources describing these early epidemics include archival materials written on parchments in Ge'ez, Ethiopia's ancient language now used primarily in Orthodox churches. Several centuries later, a Harari-Arabic manuscript recorded that a major pestilence struck the Harar area (southeastern Ethiopia) in 1261–1262 AD (Pankhurst, 1990). However, in these and other cases, the characteristics of the epidemics are not known, making it difficult to identify the diseases that caused them (Pankhurst, 1990).

From the early centuries of the first millennium (AD) smallpox (known in Amharic as *fantata/fentata*) caused the most frequent epidemic in the region (Pankhurst, 1965, 1990). The disease was first documented around 370 AD, and some historians suggest that there was a similar epidemic in 570 and 571 AD. The first definitive account of a smallpox epidemic is provided by the Scottish traveler and historian James Bruce, who learned there had been an epidemic during the reign of Emperor Iyasu I (1682–1706) as well as during his travels in Ethiopia in 1768. Subsequently, at least six smallpox epidemics were reported in the 19th century, including 1811–1812, 1838–1839, 1854, 1886, and 1889–1890 (Pankhurst, 1965, 1990). Over the centuries, multiple methods were used to prevent and treat smallpox in Ethiopia, including sudorific treatments (inducing sweating), variolation (inoculation with material taken from a recently infected individual), and more draconian methods such as isolating infected households and communities (Pankhurst, 1990, 1965). A similar traditional prevention method known as *wusheba* was used as an approach for reducing the transmission of COVID-19 at its peak period (2020) in some parts of Addis Ababa. *Wusheba* involves isolating an infected person in a separate house. The infected person will receive food and hot drinks from his/her relatives until he/she is free of the disease. When the infected person is determined to have recovered, he/she will be reintegrated into the community. In some parts of Ethiopia, smallpox patients were encouraged to consume a glass of melted butter or linseed oil every morning for 8 days. If the prognosis was good, the patients were instructed to wash themselves for 12 days in a river, shave their heads, and separate from other people for an extended period (Pankhurst, 1990, 1965).

Influenza (flu) was likely responsible for several historical epidemics. The first possible record of the disease is found in Ludolf's Amharic-Latin dictionary, published in 1698; Ludolf translates the Amharic *gunfan* as "catarrhus," a term describing inflammation of the upper respiratory tract and associated with the common cold (another viral disease) as well as influenza (flu) (Pankhurst, 1990). The annals of Emperor Iyasu I refer to an epidemic in 1706 that has been attributed to influenza (Pankhurst, 1965, 1990). Another potential influenza (flu) epidemic was reported in 1747, during which many deaths led to a shortage of burial space in major towns (Pankhurst, 1990, 1965). The first medical account of an influenza (flu) epidemic in Ethiopia was documented in 1839 by a member of the French scientific mission in Adwa (Pankhurst, 1990). There were several follow-up influenza (flu) epidemics in the 20th century, including 1908 and 1914 (Pankhurst, 1990). Local communities used traditional remedies to treat influenza (flu) (Table S1), including *tena-adam* (rue, *Ruta chalepensis* [Rutaceae]) mixed with *berbere* (red chili pepper, *Capsicum annuum* [Solanaceae]), marsh-mallow (*Alcea rosea* [Malvaceae]) leaves and other ingredients, all boiled with *tej* (local mead) (Pankhurst, 1977). Another concoction was made from the roots of a plant called *yebeg lat* (meaning "sheep's tail"); today, this name is frequently associated with *Plantago lanceolata* (Plantaginaceae) (Hedberg et al., 2006) and *Campanula edulis* (Campanulaceae) (Asfaw, 1997; Asfaw & Tadesse, 2001). Ancient sources documented that the species known by this vernacular name was drunk and rubbed on the body as a cathartic (Pankhurst, 1977). Since the former species is also listed as an antiviral medicinal plant (Table S2), it is more likely that the vernacular name refers to *P. lanceolata*, though field interviews are necessary for confirmation.

The 1918 pandemic of Spanish influenza (*yehidar beshita*) spread to the whole world in less than 6 months (Patterson & Pyle, 1991), killing tens of millions of people, even more than the bubonic plague of the 14th century (Patterson & Pyle, 1991; Taubenberger & Morens, 2006). Ethiopia experienced the Spanish flu in two waves, in the summer and autumn of 1918. The more impactful second wave peaked in October and November, hence the disease became known as *yehidar beshita* ("the November disease") (Kitaw & Kaba, 2018; Pankhurst, 1977). The death rate was extremely high, resulting in at least 50,000 deaths across the country (Kitaw & Kaba, 2018). Although there was no cure for the disease until a vaccine was developed, local people used *Eucalyptus* leaves, which they boiled in water and applied as a disinfectant. In some parts of the country, people also burned *Eucalyptus* leaves to purify the air. People also treated the Spanish flu with the local alcoholic spirit *areki* (*areke*), which is prepared by a traditional distillation process from local cereals (most often barley, but also wheat, maize, millet, or sorghum) mixed with the brewing agent known as *gesho* (*Rhamnus prinoides* [Rhamnaceae]) (Lemi, 2020) and a grain leguminous crop known as *gibto* (lupin, *Lupinus albus*).

Rabies, another viral disease, is common in Ethiopia but has rarely taken on the proportion of an epidemic (Pankhurst, 1970). Some Europeans who visited Ethiopia in the 19th century, such as Ruppell Rochetd'Hericourt, and Antoine d'Abbadie reported that rabies was more widespread in Ethiopia than in the Middle East, while others (e.g., Alfred Coubon and Walter Plowden) reported it was relatively rare (Pankhurst, 1990). Rabies was common enough that the royal court employed a traditional healer who provided treatment free of charge. The first record of a rabies epidemic in Addis Ababa dates to August 1903. Ethiopians use a variety of treatments to cure rabies, including many medicinal plants (Pankhurst, 1970). Pankhurst (1990) reported about 50 medicinal plant species that were historically used to treat rabies; however, our analyses reduced this list to 38, as some were synonymous (Table S1).

To summarize, the history of epidemics establishes that Ethiopians have experience in preventing and treating viral diseases. Traditional medical knowledge and plant resources might therefore serve as a source of innovative therapies to treat emergent viral diseases including COVID-19.

3 | ANTIVIRAL PLANTS OF ETHIOPIA

Many plants and the ailments they are used to treat have long-established vernacular names, some originating from the classical and liturgical language Ge'ez, which is mainly used in the Ethiopian Orthodox Tewahedo Church, and others from the diverse indigenous languages spoken in the country (Duressa, 2016; Pankhurst, 1990). Although many rural communities know how to use the leaves, roots, flowers, stem & root barks, seeds, or fruits of local plants to treat common ailments, most rely on traditional healers who specialize in the identification, preparation, and use of medicinal plants (Pankhurst, 1990). Our review of the literature for antiviral plants has identified 387 species belonging to 271 genera in 96 families (Table S2) used to prevent or treat eight viral diseases and nine symptoms frequently associated with viral agents (Figure 1). The largest proportion of plant species (67, 17.2%) was used for the treatment of rabies, followed by coughs, which are often caused by viral diseases, (65, 16.7%), and the common cold (58, 14.9%). Furthermore, of the 449 reported uses of plants, 12 (2.7%) address diseases or symptoms affecting the respiratory system, the major causes of morbidity for victims of the COVID-19 pandemic, particularly for elderly people (Nishiga et al., 2020; WHO, 2020a, 2020b).

Most preparations of medicinal plants used to treat viral diseases and symptoms associated with viral diseases involve pounding and crushing the plant material prior to use (344 plants, 93.2%) (Figure 2). For example, pounding the resin of *Boswellia papyrifera* (Burseraceae) and drinking the decoction are reported for the treatment of cough (Worku & Bantihun, 2018). Likewise, the traditional practice of pounding and drinking the root powder decoction of *A. abyssinica*. (Asteraceae) was mentioned as an important treatment to avert ailments of the breathing system (Abate, 1989). Our findings showed that many preparations were made by combining medicinal plants (45 plants, 12.2%). The dominant use of these types of preparations is based on many years of use and indigenous knowledge regarding the efficacy of preparations (Pankhurst, 1977). In addition, the use of additives was reported to improve the taste or to reduce the side effects of the traditional remedies. The most commonly reported additives were water (used to prepare 19.5% of the plants), honey (7.3%), butter (6.5%), egg (3.5%), coffee (2.2%), and milk (1.9%).

Medicinal plants are prepared and administered based on the recommendations of a traditional healer or self-prescription based on individual experience, notably by knowledgeable elderly men and women. Most plants are administered orally (306 species, 78.66%), followed by plants that are administered nasally (15, 3.86%), or both orally and nasally (10, 2.57%) (Figure 3). These methods of administration are traditionally determined after visual inspection of patients by local healers or elders who have developed the knowledge and skills

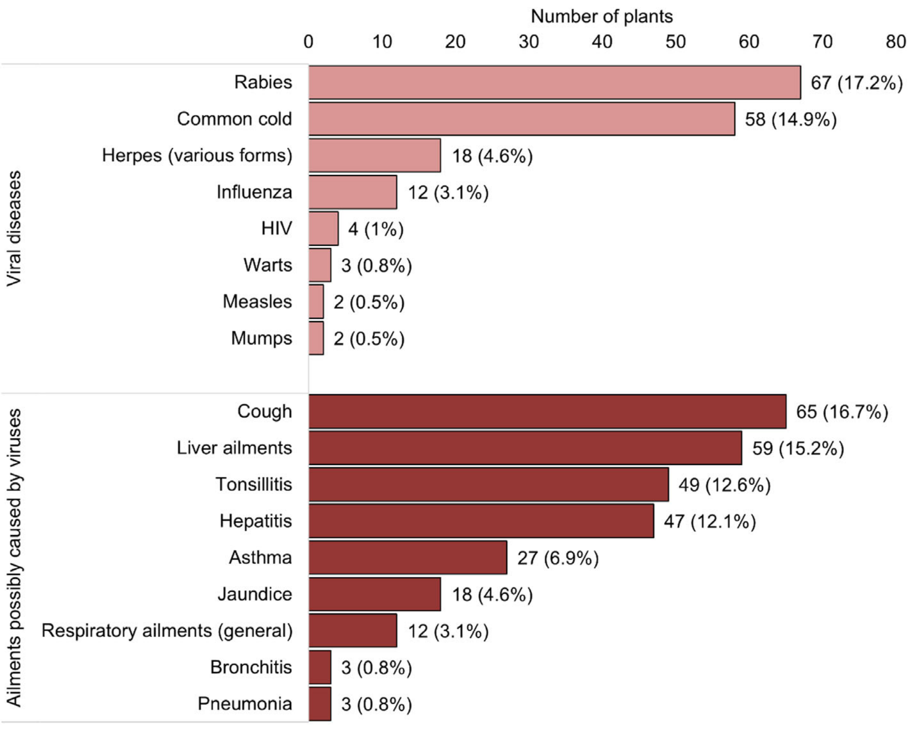


FIGURE 1 Number of medicinal plants used to treat viral diseases and ailments possibly caused by viruses in Ethiopia's traditional healing system; numbers in parentheses indicate the percent of all antiviral plant species ($n = 387$) compiled in this research.

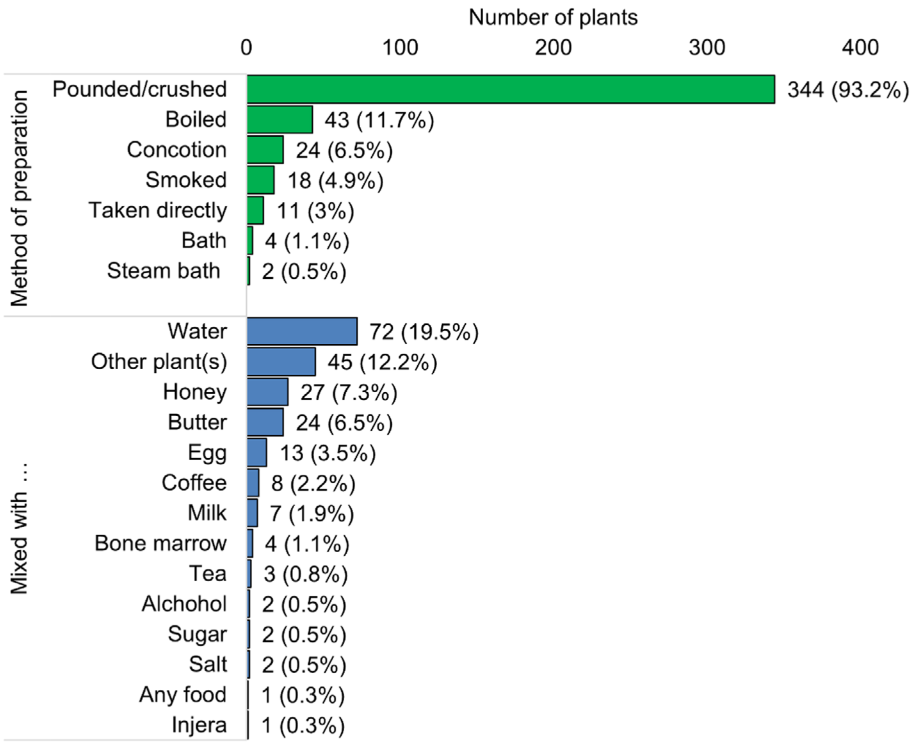


FIGURE 2 Method of preparing medicinal plants for use in treating viral diseases or symptoms in Ethiopia. Numbers in parentheses indicate the percent of all antiviral plant species ($n = 387$) compiled in this research. (*injera* is a thin spongy bread made from fermented *teff*, sorghum, or other cereals).

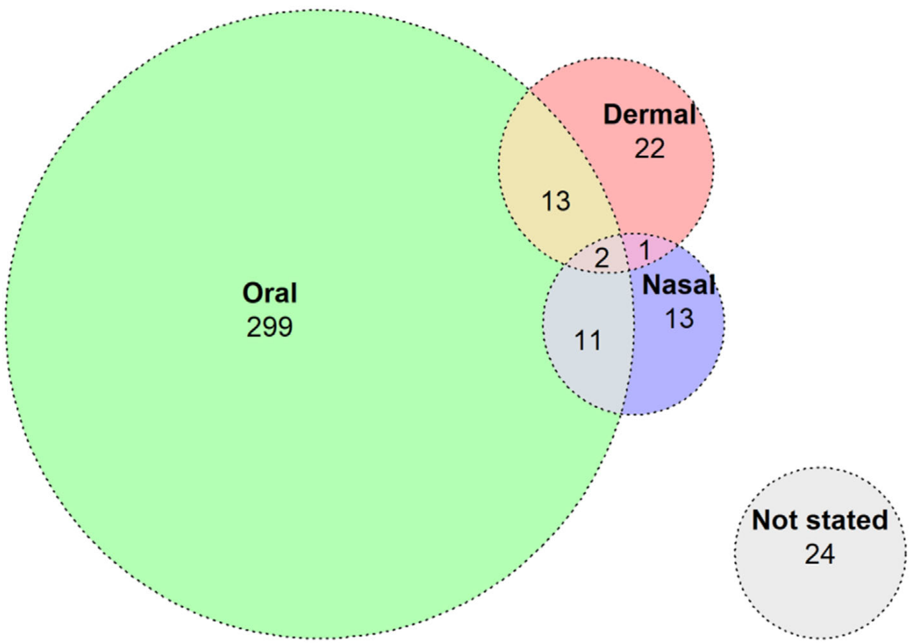


FIGURE 3 Venn diagram of methods applying medicinal plants to treat viral diseases or associated symptoms in Ethiopia. Numbers indicate the number of all antiviral plant species ($n = 385$) compiled in this study.

over years of practice. Ethnobotanical works in Ethiopia reported that local healers detect changes in body temperature, skin and eye color, appetite, and physical appearance of their patients (Giday et al., 2003; Mesfin et al., 2009; Yineger & Yewhalaw, 2007) as traditional means of disease diagnosis. These practices may lack precision and standardization, which are the global drawbacks of traditional medical systems (Abdel-Aziz et al., 2016), highlighting the need for further scientific validation, optimization, and modernization of medicinal plant utilization in the country.

Altogether, 62 species were used to prevent and treat the common cold and/or influenza (flu). These are the most promising targets for further pharmacological investigations to identify antiviral agents to combat emergent viral diseases like COVID-19 and its recently isolated variants. Based on citation frequency, 21 species were reported more than five times. The species *Zingiber officinale* (Zingibiraceae) received the highest citation score (13), followed by four species that were each cited 11 times: *Allium sativum* (Alliaceae), *Croton macrostachyus* (Euphorbiaceae), *Ocimum lamiifolium* (Lamiaceae), and *Ruta* *chalepensis*. In addition, *Justicia schimperiana* (Acanthaceae), *Nigella sativa* (Ranunculaceae), *Phytolacca dodecandra* (Phytolaccaceae), and *Solanum incanum* (Solanaceae) were each cited nine times, and 12 species were cited between seven and five times and the rest between four and one times (Table 1). The most frequently cited species are not necessarily the most effective medicinal plants, but their widespread use serves as some indication of high potential and requires further investigation.

TABLE 1 List of the most cited antiviral medicinal plants and the number of times each was mentioned in the literature sources reviewed.

No.	Species name	Citation frequency
1	*Zingiber officinale* Roscoe	13
2	*Allium sativum* L.	11
3	*Croton macrostachyus* Del	11
4	*Ocimum lamiifolium* Hochst. ex Benth.	11
5	*Ruta chalepensis* L.	11
6	*Justicia schimperiana* (Hochst. ex Nees) T. Anders.	9
7	*Nigella sativa* L.	9
8	*Phytolacca dodecandra* L.	9
9	*Solanum incanum* L.	9
10	*Eucalyptus globulus* Labill	7
11	*Lepidium sativum* L.	7
12	*Ricinus communis* L.	7
13	*Carica papaya* L.	6
14	*Rumex nepalensis* Spreng.	6
15	*Verbena officinalis* L.	6
16	*Clerodendrum myricoides*	5
17	*Cordia africana* Lam.	5
18	*Euphorbia abyssinica* Gmel	5
19	*Foeniculum vulgare* Miller	5
20	*Momordica foetida* Schumach.	5
21	*Nicotiana tabacum* L.	5

4 | PHYTOCHEMISTRY AND PHARMACOLOGY OF ETHIOPIAN TRADITIONAL ANTIVIRAL PLANTS

This study has also attempted to review published studies on in vitro antiviral activities of plants that were reported for their traditional uses to treat viral diseases in Ethiopia. Fifty-eight species belonging to 35 plant families were reviewed, of which Asteraceae 6 (17.14%), Euphorbiaceae 5 (14.29%), and Lamiaceae 3 (8.57%) were best represented (Table S3). It is widely known that more commonly available plants (in the landscape and/or at local markets) are more likely to be used for traditional treatments (Mesfin et al., 2009). Of the 58 medicinal plant extracts tested, 10 (17%) showed very good antiviral activity against viruses, with half maximal inhibitory concentration (IC_{50}) value below 11 μg/mL (Table 2).

Rubia cordifolia, *Z. officinale*, *Eucalyptus camaldulensis*, *Eucalyptus globulus*, and *A. sativum* were reported frequently for their in vitro antiviral activities, and they were also among the potent ones (Chang et al., 2012; Rouf et al., 2020; Sabo & Knezevic, 2019; Sun et al., 2016). In these studies, the aerial part, leaf, stem, root, bark, seed, and fruit of the aforementioned plants have been used to prepare extracts using solvents such as dichloromethane, petroleum ether, ethanol, methanol, and water.

Studies commonly used cellular assays such as MTT (Asres et al., 2001), cytopathogenic effect (Romeilah et al., 2010) and plaque

TABLE 2 In vitro antiviral activity of medicinal plants in Ethiopia.

Virus	Plant name (family)	Parts used/isolated compounds	$IC_{50}/ED_{50}/EC_{50}/CC_{50}$	Reference
HSV 1	*Achyranthes aspera* (Amaranthaceae)	Leaf, Root	EC_{50} (6.8 μg/mL)	Mukherjee et al., (2013)
	Eucalyptus camaldulensis (Myrtaceae)	Leaf	IC_{50} (0.1 ± 0.08 μg/mL)	Adeniyi et al., (2015)
	Eucalyptus globulus (Myrtaceae)	Stem (essential oil)	IC_{50} (0.009%)	Achmad et al., (2014)
HSV 2	*Achyranthes aspera* (Amaranthaceae)	Leaf, Root	EC_{50} (7.8 μg/mL)	Mukherjee et al., (2013)
	Eucalyptus camaldulensis (Myrtaceae)	Leaf	IC_{50} (0.3 ± 0.02 μg/mL)	Adeniyi et al., (2015)
	Eucalyptus globulus (Myrtaceae)	Stem (essential oil)	IC_{50} (0.008%)	Achmad et al., (2014)
Coxs B3	*Acokanthera schimperi* (Apocynaceae)	Leaf, Root	IC_{50} (1.34 μg/mL)	Gebre-Mariam et al., (2006)
Parv-3	*Foeniculum vulgare* (Apiaceae)	-	EC_{50} (0.4–0.8 μg/mL)	Ozçelik et al., (2011)
Var-Zos V	*Eucalyptus camaldulensis* (Myrtaceae)	Leaf	IC_{50} (1 ± 0.03 μg/mL)	Adeniyi et al., (2015)
HCV	*Eucalyptus globulus* (Myrtaceae)	Stem	IC_{50} (10.2 μg/mL)	Achmad et al., (2014)
	Flueggea virosa (Euphorbiaceae)	Spruceanol	EC_{50} (5 μM)	Chao et al., (2016)
HCV-1	*Foeniculum vulgare* (Apiaceae)	-	EC_{50} (0.2–0.4 μg/mL)	Ozçelik et al., (2011)
Influenza virus A	*Pentanema confertiflorum* (Asteraceae)	Leaf	IC_{50} (6.5 μg/mL)	Gebre-Mariam et al., (2006)
Hep B	*Rubia cordifolia* (Rubiaceae)	Root	IC_{50} (2.0 μg/mL)	Ho et al., (1996)
Rhin IB	*Zingiber officinale* (Zingibiraceae)	β-Sesquiphellandrene	IC_{50} (0.44 μM)	Denyer et al., (1994)

reduction (Seo & Choi, 2017); and molecular assays such as RNA-dependent RNA polymerase inhibition (Jo et al., 2006), enzyme-linked immunosorbent assay (ELISA) and quantitative RT-PCR assay (Javed et al., 2011) to check the antiviral activities of the plant extracts against different viruses. Viruses such as human immunodeficiency viruses (types 1 and 2), herpes simplex viruses (types 1 and 2), coxsackievirus B, human influenza virus A (H1N1), avian influenza virus A (H5N1), and hepatitis C and B were cultured with different doses of extracts on different cell lines (Bagla et al., 2012). Frequently reported cell lines compatible with the growth of the viruses were Human T-lymphocytic MT-4 cells, Vero cells, human cervix carcinoma (HeLa) cell lines, and Madin–Darby canine kidney cell lines (Bagla et al., 2012; Cos et al., 2002). In line with this, phytochemical analyses made on Ethiopian medicinal plants over the years indicated that terpenoids and phenolic compounds (Asres & Bucar, 2005; Gebre-Mariam et al., 2006) are the major classes of secondary metabolites responsible for antiviral activities, as discussed below.

4.1 | Terpenoids

Different terpenoids such as diterpenoids, sesquiterpenoids, and triterpenoids have been reported for their antiviral activities (Wen et al., 2007). Oleanolic acid, a triterpene acid, isolated from the methanolic extract of *Achyranthes aspera* inhibited the replication of both herpes simplex type 1 (HSV-1) and 2 (HSV-2) viruses (Mukherjee et al., 2013). The methanolic extract of *Acokanthera schimperi*, collected from Ethiopia, was also reported for its anti-coxsackievirus B3 activity (Gebre-Mariam et al., 2006). According to this and other related studies (for example de Tommasi et al., 1992; Li et al., 2019), the antiviral activity of *A. schimperi* might be due to the pentacyclic triterpenoid compound, ursolic acid. The dinorditerpenoid compounds, 3β,12-dihydroxy-13-methylpodocarpa-6,8,11,13-tetraene (**1**), spruceanol (**2**), 7α,20-epoxy-3α-hydroxy-12-methoxy-13-methyl-ent-podocarp-8,11,13-triene (**3**), 3α,20-epoxy-3β-hydroxy-12-methoxy13-methyl-ent-podocarp-8,11,13-triene (**4**), and 3β,12-dihydroxy-13-methylpodocarpa 8,11,13-triene (**5**) isolated from *Flueggea virosa* have also been reported to have potent anti-hepatitis C virus activities (Chao et al., 2016). β-sesquiphellandrene, isolated from the methanol extract of another traditionally used Ethiopian antiviral plant *Z. officinale* was shown to decrease the plague count of the rhinovirus by 50% at 0.44 μM (Denyer et al., 1994) (Figure 4).

Similar studies have also reported antiviral triterpenoids from traditionally used Ethiopian plants such as *Ximenia americana* (Olacaceae) (Asres et al., 2001) and *Ekbergia capensis* (Meliaceae) (Ryu et al., 1994); and diterpenoids from *Dodonaea angustifolia* (Sapindanceae) (Ghisalberti, 1998) and *Coleus barbatus* (Lamiaceae) (Alasbahi & Melzig, 2010; Kapewangolo et al., 2013). The monoterpenoid, 1,8-cineole (eucalyptol) (**6**) which is the major component of the essential oil of *E. globulus* controls airway mucus hypersecretion and asthma via anti-inflammatory cytokine inhibition. Eucalyptol is an effective treatment for non-purulent rhinosinusitis (Juergens, 2014; Juergens et al., 2020). Cineole is the most important chemical constituent that determines the medicinal value of *Eucalyptus* oil (Shiferaw et al., 2019).

4.2 | Phenolic compounds

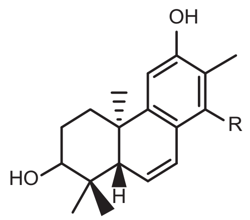
Flavonoids are the largest group of phenolic compounds with diverse biological functions in plants. Flavonoids are reported for their antiviral activities against enterovirus A71 (Lalani & Poh, 2020), dengue virus (Sánchez et al., 2000), and herpes simplex virus (Asres et al., 2001). Ombuin, a flavonol from the leaves of *Boswellia papyrifera*, has been analyzed for its antiviral activity against avian influenza virus A(H5N1) (Salem et al., 2016). The study revealed that ombuin (**7**) inhibited the replication of H5N1 by 61% at a concentration of 20 μg/mL (Salem et al., 2016). Asres et al. (2001) reported the anti-HIV-1 activity of the methanol fraction of *D. angustifolia*. 3-Methoxyflavones and other secondary metabolites were reported in relatively large quantities in the seeds, flower, and stems of *D. angustifolia*, which might be the reason for the antiviral activity (Vlietinck et al., 1995). Tannins, another group of phenolic compounds, have been reported for their antiviral activities. The antiviral activity of *E. camaldulensis* has been associated with the presence of ellagitannins in the plant.[81] Punicalagin (**8**), another ellagitannin isolated from *Combretum molle* (Combretaceae) collected from Ethiopia, demonstrated inhibition of HIV-1 replication at a 50% effective concentration of 1.2 mg/mL with a selectivity index of 16 (Asres & Bucar, 2005). On the other hand, the same compound (punicalagin) isolated from *Punica granatum* (Lythraceae) showed 100% anti-HSV-2 activity at 31.25 μg/mL (Arunkumar & Rajarajan, 2018). Mangiferin (**9**), a C-glycosylxanthone, isolated from *Mangifera indica* (Anacardiaceae) showed potent anti-acyclovir-resistant herpes simplex-1 virus activities (Rechenchoski et al., 2020). The naphthohydroquinones, furomollugin (**10**), and mollugin (**11**) isolated from *R. cordifolia* suppressed the secretion of surface antigen of hepatitis B with IC_{50} value of 2 μg/mL (Ho et al., 1996). Isolates of phenolic compounds xanthopurpurin (**12**) and vanillic acid (**13**) from the aerial part of *R. cordifolia* showed that both compounds inhibit rotavirus multiplication by promoting virus also induced apoptosis on rhesus monkey kidney cell line (MA-104) (Figure 5) (Sun et al., 2016).

4.3 | Alkaloids

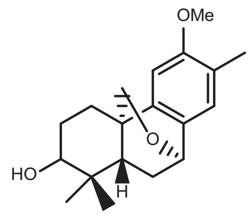
Natural alkaloids isolated from a variety of plants have been shown to exhibit potent antiviral activity toward different viruses (Ieven et al., 1982; Ozçelik et al., 2011). *Erythrina* alkaloids isolated from *Erythrina abyssinica* (Fabaceae) were shown to be responsible for the protection of MT-4 cells against HIV-1-induced cytopathogenicity (Mohammed et al., 2012).

4.4 | Organosulfur compounds

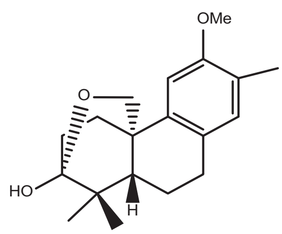
Organosulfur compounds like allicin (**14**), diallyl trisulfide (**15**), and ajoene (**16**) are the main chemicals that impart the antiviral properties of garlic (*A. sativum*). Garlic and its active organosulfur compounds (Figure 6) have been reported to alleviate several viral infections,



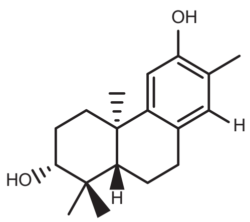
	R
3β,12-dihydroxy-13-methylpodocarpa-6,8,11,13-tetraene (**1**)	H
Spruceanol (**2**)	CH2=CH2



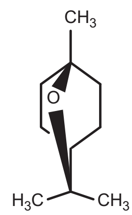
7α,20-epoxy-3α-hydroxy-12-methoxy-13-methyl-ent-podocarp-8,11,13-triene (**3**)



3α,20-epoxy-3β-hydroxy-12-methoxy13-methyl-ent-podocarp-8,11,13-triene (**4**)



3β,12-dihydroxy-13-methylpodocarpa 8,11,13-triene (**5**)



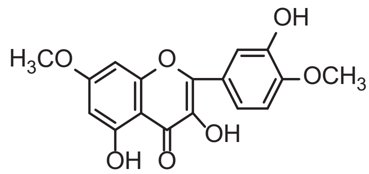
1,8-cineole (**6**)

FIGURE 4 Structures of antiviral terpenoids reported from traditional antiviral medicinal plant *Flueggea virosa*.

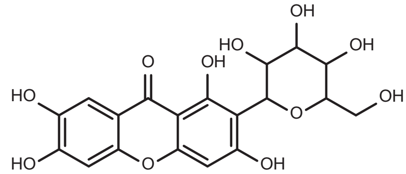
including flu and respiratory infections (Rouf et al., 2020). Garlic has been used for centuries as an ethnomedicinal plant to treat infectious diseases. The medicinal use and effectiveness of this species in Ethiopia are widely known and frequently applied not only as medicine but also as a nutraceutical plant.

The above phytochemistry and pharmacology section provided some insights into the research done so far about the antiviral plants of Ethiopia. However, the analysis showed the need for more research to fully investigate and test the antiviral properties of Ethiopian plants. Only 15% of the plants reported in our study were tested for antiviral activity against various viruses. The majority of the activities of the extracts and isolated compounds, however, were performed on in vitro assays, with no follow-up in vivo studies to validate the results. Thus, further research focusing on the validation and establishment of a database to share and exchange the already known studies would be very important in fighting and combating the existing and emergent viral diseases in Ethiopia and elsewhere.

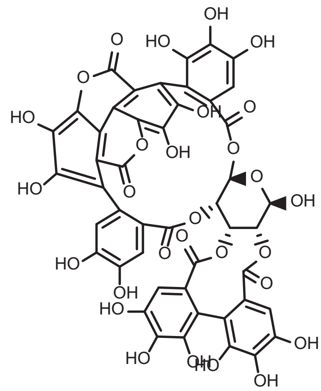
FIGURE 5 Structures of phenolic compounds reported from traditional antiviral medicinal plants of Ethiopia. Structure 7 is from *Boswellia papyrifera*, structure 8 is from *Combretum molle*, structure 9 is from *Mangifera indica*, and structures 10–13 are from *Rubia cordifolia*.



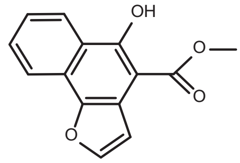
Ombuin (**7**



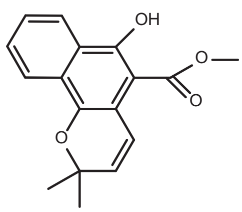
Mangiferin (**9**)



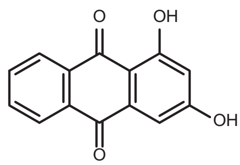
Punicalagin (**8**)



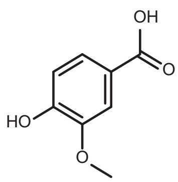
Furomollugin (**10**)



Mollugin (**11**)

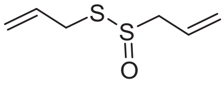


Xanthopurpurin (**12**)

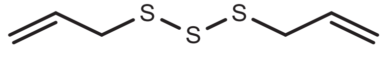


Vanillic acid (**13**)

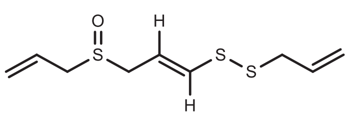
FIGURE 6 Structures of organosulfur compounds reported from the traditional antiviral medicinal plant *Allium sativum*.



Allicin (**14**)



Diallyl trisulfide (**15**)



Ajoene (**16**)

5 | CONCLUSION

Our review of medicinal plants used to treat and prevent viral diseases in the Ethiopian traditional herbal medicine system reveals the presence of a considerable number (387) of traditionally useful medicinal plants and associated indigenous and local knowledge that might be used to address emergent viral diseases in Ethiopia and elsewhere. Chemical elucidation of a limited number (58) of the antiviral plants tested so far has shown encouraging results for combating antiviral diseases in addition to the consensus among traditional herbal medicine practitioners. However, the proportion of antiviral plants adequately tested in controlled laboratory and clinical settings to determine their efficacy and/or toxicity *vis-à-vis* the species compiled in this study is infinitesimally small. Hence, it is imperative to begin testing the most promising Ethiopian antiviral plants, beginning with those that have been cited in five or more of the manuscripts (Table 1) that were systematically reviewed in this study.

Ethiopian traditional medicine in general and the use of plants as antivirals in particular raise many important questions about how to integrate traditional knowledge and experience in combination with scientific data to promote the public health benefits of promising species and the associated indigenous and local knowledge. We propose the following steps to incorporate indigenous and local knowledge associated with medicinal plants including the antivirals into Ethiopia's national healthcare delivery system and the education sector to forge a sustainable future:

- Documentation of medicinal plants used across Ethiopia is incomplete. To remedy this situation, systematic research with traditional healers, as well as a platform to convene healers from Ethiopia's diverse cultural traditions would facilitate the collective identification, validation, and prioritization of the most effective medicinal plants requiring further investigation on antiviral and other medicinal plants.
- A multidisciplinary and multistakeholder approach involving ethnobotanists, herbalists, microbiologists, clinicians, pharmacologists, chemists, conservationists, traditional healers, and other stakeholders should be engaged at different levels to develop new alternative models to assess the benefits and risks of promoting the use of medicinal plants to effectively prevent or treat existing and emergent viral diseases. The model/flow diagram ahead (Figure 7) hints at the main actors and activities that are required to institute a system for dealing with the issues of antiviral medicinal plants and the associated knowledge systems. To this end, we support the establishment of a well-coordinated multidisciplinary Institute for the study of medicinal plants. One of the priority engagements of this proposed new institute should be developing new technologies for the treatment and prevention of emergent viral diseases based on a combination of traditional knowledge and scientific trials, focusing on in vivo studies of those plant products whose in vitro activities are well-established and others in a prioritized manner.

Already, the expansion of croplands due to rapid population growth and extensification of agriculture is reducing the availability of medicinal plants routinely gathered from natural forests, woodlands, and grasslands. To safeguard wild plant populations and promote their sustainable use as health resources and combat existing and future viral epidemics and pandemics, we suggest:

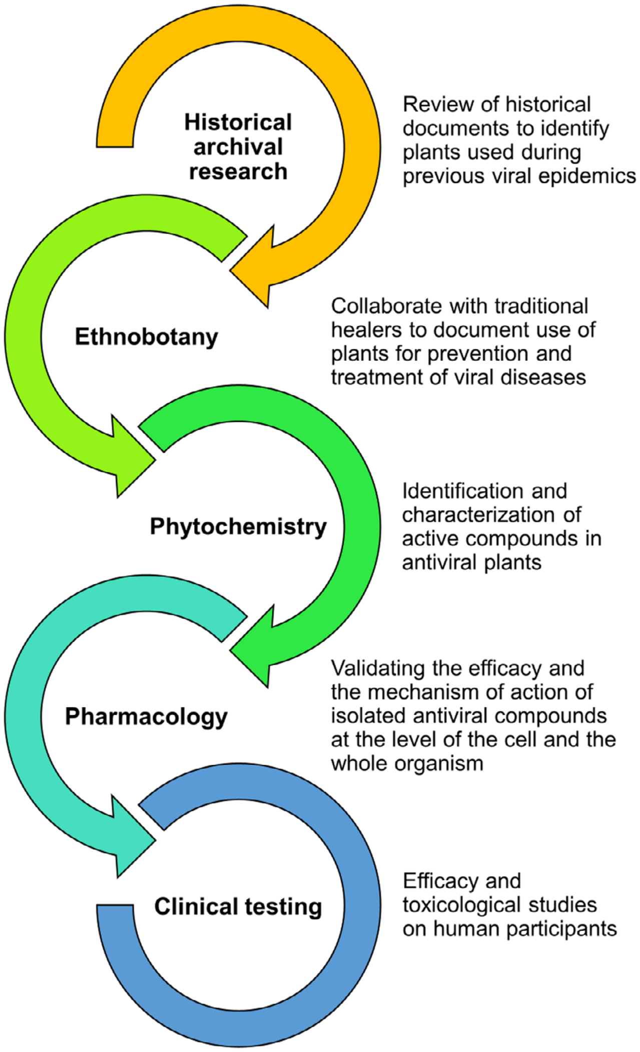


FIGURE 7 An interdisciplinary model to prioritize medicinal plants for research and development of antiviral therapies.

- A strong organizational structure and a proactive national commitment charged with the task of implementing conservation plans targeting the traditional medicinal plants in Ethiopia are urgently needed. This would need consideration of and enhancement of national and community medicinal plant seed banks alongside those already established for agricultural (grain) crops. Populations of antiviral medicinal plants should be continuously monitored and conserved both in situ and ex situ.
- New regulations and enforcement mechanisms are necessary to promote and maintain stewardship practices based on traditional medicinal knowledge.

Overall, our review highlights the available resources and the need to connect indigenous knowledge with formal science to combat existing and emergent viral diseases in Ethiopia and elsewhere. Deeper collaboration between scientists and indigenous experts in antiviral research promises to advance both cultural traditions and public health.

AUTHOR CONTRIBUTIONS

Mekbib Fekadu: Conceptualization; data curation; formal analysis; investigation; methodology; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Ermias Lulekal:** Conceptualization; data curation; formal analysis; investigation; methodology; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Solomon Tesfaye:** Conceptualization; data curation; formal analysis; investigation; methodology; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Morgan Ruelle:** Conceptualization; data curation; formal analysis; investigation; methodology; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Nigist Asfaw:** Resources; writing – review and editing. **Tesfaye Awas:** Resources; writing – review and editing. **Kebu Balemie:** Data curation; resources; writing – review and editing. **Kaleab Asres:** Resources; writing – review and editing. **Sebastian Guenther:** Resources; writing – review and editing. **Zemede Asfaw:** Resources; writing – review and editing. **Sebsebe Demissew:** Resources; writing – review and editing.

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The authors declare no competing interests.

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