Herbs for Emerging Viral Infectious Diseases

Eric Yarnell, ND, RH (AHG)

Abstract

Several coronavirus (severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), flavivirus (yellow fever, West Nile, dengue, Zika), and alphavirus (chikungunya, Ebola) infections have, in the past 10–20 years, emerged or reemerged as major problems across large regions of the globe. While, currently, many of these infections are confined to the tropics, global warming, the spread of some mosquito vectors northward, and emergence of temperate-tolerant pathogens such as West Nile virus mean that these problems are increasingly affecting the global north as well. After discussing mosquito-based preventions for the zoonotic infections mentioned in this article, a review of herbal responses to the SARS and MERS epidemics are highlighted. *Houttuynia cordata* (houttuynia, *yú xīng cǎo*) and *Glycyrrhiza* spp. (licorice) stand out as particularly interesting single herbs for addressing these coronavirus infections. Herbal approaches to flavivirus infections, most notably clinical trials of *Carica papaya* (papaya) leaves for treating dengue fever, are reviewed. A discussion of many of the extensive range of herbs studied to treat flaviviruses in preclinical studies is provided. Potential herbal treatments for alphavirus infections are then presented.

Introduction

Emerging pathogens are big news. Whether it is West Nile, severe acute respiratory syndrome (SARS), Ebola, Zika, or any of the other many diseases in the headlines, public health officials, practitioners, and ordinary people take notice. It was just a few decades ago that human immunodeficiency virus (HIV) went from being an unknown to an exotic emerging infection to a global pandemic that, according to the World Health Organization, as of 2013, had infected 78 million people and killed 39 million worldwide.[1] Knowledge, preparation, and prevention should be the key words when it comes to emerging infections. Unfortunately, these problems tend to receive low priority in government and research budgets (given the existence of bigger problems and priorities in most places), and once the news becomes stale, interest and funding tend to dry up.

Most emerging infections are direct threats to middle- and low-income countries, with only a handful of cases affecting travelers returning to North America and Europe, directly impacting countries there. Concern about these pathogens should not eclipse clear and present dangers that have become humdrum yet still cause enormous suffering and death, most notably influenza. Every year, this causes two epidemics (one per hemisphere) with 3–5 million severely impacted patients and causes a total of 500,000 deaths, tens of thousands of which occur in the United States.[2,3] This occurs despite the widespread availability of vaccines (albeit of variable efficacy each year) and several types of effective drugs and herbs for treatment of infected people. The totality of all deaths from the highly publicized 2014 West African Ebola, 2012 Middle East respiratory syndrome (MERS), and 2002 SARS epidemics combined do not equal an average year's worth of influenza deaths.

Nevertheless, emerging infections cannot be ignored or characterized accurately by body counts alone. The 2014 West Africa Ebola virus was devastating to the already fragile economies of Guinea, Sierra Leone, and Liberia, having an impact far beyond the numbers those infected or killed. Ultimately, this affected the United States, because it was much more expensive and difficult to intervene late in the crisis than it would have been if research had been ongoing since it became clear that Ebola was not going away (as early as the 2000 Uganda outbreak that killed 224 people, but certainly by the time of the 2007 outbreaks in Uganda and the Democratic Republic of the Congo in which another 224 people died).[4] Instead, the United States alone spent $1.4 billion once the crisis was already well-advanced.[5]

All of the major emerging pathogens discussed in this article (see Table 1) are group IV retroviruses with (+)ssRNA genomes. Many other pathogens could be discussed, but as a group these may all be susceptible to similar herbal therapies.

Methods of avoiding the bites of mosquitoes that transmit many emerging infectious organisms, as well as serious established ones such as malaria, can be found in previously published work.[6] Prevention of mosquito bites, as well as limiting mosquito reproduction, is crucial to preventing these illnesses. In many cases, such as Zika virus, when the emergence is so new that essentially no information is available concerning treatment, this is the only evidence-based natural

Table 1. Summary of Emerging ssRNA Virus Infections

Infectious organism (vector)	Genus	Vaccine?	Herbal treatment status
Coronaviruses			
SARS-CoV (none)	Betacoronavirus	None	Clinical trials
MERS-CoV (none)	Betacoronavirus	None	In vitro
Flaviviruses			
West Nile virus (mosquitoes, *Culex* spp. in United States)	Flavivirus	None	In vitro
Dengue virus (mosquitoes, especially *Aedes aegypti*)	Flavivirus	Yes (approved but not commercially available yet), only 60% effective[a]	In vitro
Yellow fever virus (mosquitoes, especially *Aedes aegypti*)	Flavivirus	Yes, highly effective	In vitro
Zika virus (*Aedes* mosquitoes)	Flavivirus	None	None
Miscellaneous			
Chikungunya virus (mosquitoes, especially *A. aegypti*)	Alphavirus	None	In vitro
Ebola virus (none)	Ebola virus	None	In vitro

[a]Ref. 26.
SARS, Severe acute respiratory syndrome; MERS, Middle East Respiratory Syndrome.

option available for preventing infection. Some updated reports of herbs that can inhibit mosquito virus replication or repel mosquitoes since the 2004 publication[6] are given in Table 2. It should also be noted there has been success with deliberately infecting *Aedes aegypti* mosquitoes with the intracellular bacterium *Wolbachia pipientis* strain wMel in order to block both dengue and chikungunya viruses from being able to infect the mosquitoes.[7] This intriguing, nonchemical approach to mosquito control deserves increased research attention.

The cycle of developing drugs and vaccines is simply too slow to address most emerging infectious diseases. Instead, natural products should be prioritized, as their safety is already established, their efficacy has been shown in preliminary reports for several infectious diseases of concern, and they are much more readily available. This is not to say that no effort should go into vaccine research in particular, but less emphasis should be put on drug research, which is usually too slow to address a new outbreak. In the case of dengue, for example, despite more than 10 years of research on drugs for treating the condition, no effective treatments been found and those drugs that have entered clinical trials have been too toxic and/or ineffective.[8] A vaccine candidate has emerged, but by all accounts it is $< 60\%$ effective (see Table 1).

The information given here documents research which supports that natural products can be effective responses to emerging infections. These products are readily available and promising, and so research should focus on clarifying the optimal extracts, doses, and duration of use for these agents in humans over synthetic drugs until—and unless—better options can be proven. In the midst of a crisis with no established effective vaccine or drug, use of natural products should be promoted to give patients the best chances of recovery and survival. Natural products may not always be sufficient, and in some cases may not work at all, but it is almost certainly better to at least consider this option rather than largely ignoring it or doing nothing.

Coronaviruses: SARS and MERS

SARS emerged in southern China (particularly in Hong Kong) in November of 2002.[9] Clinically, patients developed a fever and flulike illness 2–10 days after exposure. The group IV coronavirus that causes this infection—now dubbed SARS-CoV—was identified, and its single-stranded RNA genome was characterized by April 2003. In the one and only known outbreak of this disease, nearly 10,000 people were infected in numerous countries with just under 1000 deaths.[1] It is now known to be a zoonotic disease that infects and is spread by several animals, including palm civets and bats. Although it was feared that this outbreak could become a much wider problem, it never did so and it has not recurred. No vaccine was developed, but, ultimately, the outbreak was stopped by early case identification, isolation, and careful precautions—including protecting healthcare workers—against spreading the organism.[10]

During the outbreak in Hong Kong, a cohort of hospital healthcare workers volunteered to take an herbal formula developed to prevent SARS infection; the formula combined two famous traditional Chinese formulas for respiratory infections—*sāng jú yǐn* (Mulberry and Chrysanthemum Drink, a formula developed in 1798) and *yù píng fēng sǎn* (Jade Windscreen Powder, from either 1213 or 1481)—and two known antiviral herbs.[11] The final formula (ratios and exact amounts were not given) included *Morus alba* (mulberry, *sāng yè*) leaf,

Table 2. Recently Reported Herbs Against Mosquitos and Mosquito Larvae Transmitting Emerging Infectious Viruses

Herb, extract, or constituent	Effect	Reference
Camellia sinensis (green and black tea) leaf	Aqueous extract larvicidal against *Aedes aegypti*, inhibited pupation	Dieng et al., 2016[a]
Cinnamomum verum (true cinnamon) volatile oil	Repellant against adult *A. aegypti* mosquito	Prajapati et al., 2005[b]
Curcuma longa (turmeric) rhizome volatile oil	Larvicidal against *A. aegypti*; repellant against adult *A. aegypti* mosquito for 150 minutes with 5% vanillin	Kalaivani et al., 2012[c]; Auysawasdi et al., 2016[d]
Eucalyptus spp. leaf volatile oil 15% + vanillin 5%	Repellant against *Aedes albopictus* bites for 5 hours in humans	Yang & Ma, 2005[e]
Lantana camara (big sage) hexane extract	Larvicidal against *A. aegypti* (also volatile oil); repellant against adult *A. aegypti* mosquito for 150 minutes combined with methanol extract of *Ocimum gratissimum* (clove basil) in humans	Sharma et al., 2016[f]; Kumar et al., 2012[g]; Keziah et al., 2015;[h] Hemalatha et al., 2014[i]
Ligusticum sinense (Szechuan lovage, *chuān xiōng*) root	Ethanol extract 25% prevented *A. aegypti* biting for 6.5 hours in humans (11 hours when 5% vanillin was added); also very repellant against *Anopheles* mosquito (malaria vector)	Sanghong et al., 2015[j]
Mentha spicata (spearmint) leaf volatile oil	Larvicidal against *A. aegypti*	Govindarajan et al., 2012[k]
Mentha x *piperita* (peppermint) leaf volatile oil	Inhibits egg laying by *A. aegypti*; ovicidal and larvicidal against *A. aegypti*; repellant against adult *A. aegypti* mosquito	Kalaivani et al., 2012[c]; Kumar et al., 2011[l]; Warikoo et al., 2011[m]
Zingiber nimmonii (*mala-inchi*) rhizome volatile oil	Larvicidal against *A. aegypti*; repellant against adult *A. aegypti* mosquito	Govindarajan et al., 2016[n]
Zingiber officinale (ginger) rhizome volatile oil	Larvicidal against *A. aegypti*; repellant against adult *A. aegypti* mosquito	Kalaivani et al., 2012[c]; Boonyan et al., 2014[o]

[a]Dieng H, Tan Yusop NS, Kamal NN, et al. Exposure of a dengue vector to tea and its waste: Survival, developmental consequences and significance for pest management. *J Agric Food Chem* 2016;64:3485–3491; [b]Prajapati V, Tripathi AK, Aggarwal KK, Khanuja SP. Insecticidal, repellent and oviposition-deterrent activity of selected essential oils against *Anopheles stephensi*, *Aedes aegypti* and *Culex quinquefasciatus*. Bioresour Technol 2005;96:1749–1757; [c]Kalaivani K, Senthil-Nathan S, Murugesan AG. Biological activity of selected Lamiaceae and Zingiberaceae plant essential oils against the dengue vector *Aedes aegypti* L. (Diptera: Culicidae). Parasitol Res 2012;110:1261–1268; [d]Auysawasdi N, Chuntranuluck S, Phasomkusolsil S, Keeratinijakal V. Improving the effectiveness of three essential oils against *Aedes aegypti* (Linn) and *Anopheles dirus* (Peyton and Harrison). Parasitol Res 2016;115:99–106; [e]Yang P, Ma Y. Repellent effect of plant essential oils against *Aedes albopictus*. J Vector Ecol 2005;30:231–234; [f]Sharma A, Kumar S, Tripathi P. Evaluation of the larvicidal efficacy of five indigenous weeds against an Indian strain of dengue vector, *Aedes aegypti* L (Diptera: Culicidae). J Parasitol Res 2016;2016:2857089; [g]Kumar S, Wahab N, Mishra M, Warikoo R. Evaluation of 15 local plant species as larvicidal agents against an Indian strain of dengue fever mosquito, *Aedes aegypti* L (Diptera: Culicidae). Front Physiol 2012;3:104; [h]Keziah EA, Nukenine EN, Danga SP, et al. Creams formulated with *Ocimum gratissimum* L and *Lantana camara* L crude extracts and fractions as mosquito repellents against *Aedes aegypti* L (Diptera: Culicidae). J Insect Sci 2015;15:pii:45; [i]Hemalatha P, Elumalai D, Vignesh A, et al. Bioefficacy of essential oils of *Lantana camara* aculeata, against *Aedes aegypti*, *Anopheles stephensi* and *Culex quinquefasciatus*. Int J Pure Appl Zool 2014;2:329–338; [j]Sanghong R, Junkum A, Chaithong U, et al. Remarkable repellency of *Ligusticum sinense* (Umbelliferae), a herbal alternative against laboratory populations of *Anopheles minimus* and *Aedes aegypti* (Diptera: Culicidae). Malar J 2015;14:307; [k]Govindarajan M, Sivakumar R, Rajeswari M, Yogalakshmi K. Chemical composition and larvicidal activity of essential oil from *Mentha spicata* (Linn) against three mosquito species. Parasitol Res 2012;110:2023–2032; [l]Kumar S, Wahab N, Warikoo R. Bioefficacy of *Mentha piperita* essential oil against dengue fever mosquito *Aedes aegypti* L. Asian Pac J Trop Biomed 2011;1:85–88; [m]Warikoo R, Wahab N, Kumar S. Oviposition-altering and ovicidal potentials of five essential oils against female adults of the dengue vector, *Aedes aegypti* L. Parasitol Res 2011;109:1125–1131; [n]Govindarajan M, Rajeswary M, Arivoli S, et al. Larvicidal and repellent potential of *Zingiber nimmonii* (J Graham) Dalzell (Zingiberaceae) essential oil: An eco-friendly tool against malaria, dengue, and lymphatic filariasis mosquito vectors? Parasitol Res 2016;115:1807–1816; [o]Boonyuan W, Grieco JP, Bangs MJ, et al. Excito-repellency of essential oils against an *Aedes aegypti* (L) field population in Thailand. J Vector Ecol 2014;39:112–122.

Chrysanthemum morifolium (yellow chrysanthemum, *huáng jú huā*) flower, *Prunus armeniaca* (bitter apricot, *kǔ xìng rén*) seed, *Forsythia suspensa* (forsythia, *lián qiào*) fruit, *Mentha haplocalyx* (wild mint, *bò hé*) leaf, *Platycodon grandiflorus* (balloon flower, *jié gěng*) root, *Glycyrrhiza uralensis* (licorice, *gān cǎo*) root, *Phragmites australis* (reed, *lú gēn*) rhizome, *Astragalus membranaceus* (astragalus, *huáng qí*) root, *Saposhnikovia divaricata* (ledebouriella, *fáng fēng*) root, *Isatis tinctoria* (wild indigo, *bǎn lán gēn*) leaf, and *Scutellaria baicalensis* (Chinese skullcap, *huáng qín*) root.

A group of 1063 workers took the herbal formula once daily (dose and dose form not specified) for 2 weeks and were compared to 15,374 healthcare workers who did not take the formula. None of the workers who took the herbal formula developed SARS, compared to 64 (0.4%) of those who did not take the formula, a statistically significant difference. There were 19 minor and no serious adverse effects in the workers who took the herbal formula. Although the methodology of this trial was weak, it provided a promising basis for future studies if another outbreak should occur.

A group of 123 patients with SARS at a hospital in Beijing were all treated with oxygen, hemofiltration, ribavirin, azithromycin, cefuroxime, metronidazole, thymosin (an immunomodulator), and corticosteroids (if indicated clinically) and were randomized to that treatment alone (control) or the addition of an injectable form of *Houttuynia cordata* (houttuynia, *yú xīng cǎo*) herb.[12] Additional oral herbs were given as indicated for specific patients in the combination therapy group. Results were only available for 115 of the original cohort. There was no difference in mortality between the groups; 5 died in the combination group, compared to 7 in the Western medicine–only group. Arthralgia and myalgia were significantly less severe in the combination group, compared those treated with Western medicine only. Yet, duration of hospital stay was actually significantly longer in the combination group, compared to the control group.

One in vitro study found that houttuynia both induced immune changes and inhibited SARS-CoV protease and polymerase.[13] There is evidence of houttuynia protecting cells against other coronaviruses as well.[14] It is similarly speculative if *Anemopsis californica* (yerba mansa) root—which is in the same botanical family as houttuynia, the Saururaceae—might also be helpful. It is a traditional medicine used to address many infectious diseases in western America and Mexico. Only time and research will tell.

Numerous herbs have shown activity against SARS-CoV in vitro. *Rheum palmatum* (rhubarb) root and *Polygonum multiflorum* (*he shou wu*) root were both found to inhibit SARS-CoV binding to angiotensin converting enzyme 2, which is a major receptor by which this virus enters cells.[15] Emodin, an anthraquinone glycoside from both of these plants, was shown to be a crucial factor in blocking viral entry.

Glycyrrhiza glabra (licorice) and *G. uralensis* (*gān cǎo*, Asian licorice) root are important antiviral herbs.[16] Glycyrrhizin is the principal triterpenoid glycoside in these herbs, and showed early promise in inhibiting SARS-CoV.[17] In a comparative study in vitro, glycyrrhizin was more effective than several antiviral drugs, such as ribavirin, for inhibiting SARS-CoV replication.[18] Promising variants of glycyrrhizin have been synthesized with even more anti-SARS-CoV activity.[19] Additional reports of natural products active against SARS-CoV are noted in Table 3.

The MERS coronavirus (MERS-CoV) is a betacoronavirus that first emerged in humans in Saudi Arabia in 2012.[20] MERS was soon noted in patients in surrounding countries including Qatar, Oman, the United Arab Emirates, and Jordan. This outbreak was largely confined to elderly patients and those who had serious underlying health problems causing them to be immunocompromised. Camels were likely intermediate hosts. All of this closely mirrored the SARS outbreak 10 years earlier, except MERS did not infect as many people, nor did it infect relatively healthy people. The dipeptidyl peptidase IV has been identified as the cellular receptor for MERS-CoV.

Flaviviruses: Dengue, West Nile, Yellow Fever, and Zika

Flaviviruses are a group of extremely problematic diseases spread by mosquitoes. The oldest scourge among them, yellow

Table 3. Miscellaneous Herbal Inhibitors of SARS-CoV

Herb	Extract or compound	Reference
Aesculus hippocastanum (horse chestnut)	Aescin	Wu et al., 2004[a]
Cimicifuga simplex (bugbane, *shēng má*)	Methanol extract	Kim et al., 2008[b]
Cinnamomum spp. (cinnamon)	Aqueous extract	Zhuang et al., 2007[c]
Cinnamomum spp. (cinnamon)	Butanol extract, proanthocyanidins	Zhuang et al. 2009[d]
Coptis chinensis (goldthread, *huáng lián*)	Methanol extract	Kim et al., 2008[b]
Melia toosendan (chinaberry bark, *kǔ liàn pí*)	Methanol extract	Kim et al., 2008[b]
Numerous	Luteolin	Yi et al., 2004[e]
Phellodendron amurense (Amur corktree, *huáng bǎi*)	Methanol extract	Kim et al., 2008[b]
Rauvolfia serpentina (Indian snakeroot)	Reserpine	Wu et al., 2004[a]
Rhus sinensis (Chinese sumac, nutgall tree)	Ethanol extract, tetra-*O*-galloyl-β-d-glucose	Yi et al., 2004[e]
Scutellaria baicalensis (*huáng qín*, Baikal skullcap)	Baicalin	Chen et al., 2004[f]
Sophora subprostrata (bushy sophora, *shān dòu gēn*)	Methanol extract	Kim et al., 2008[b]
Syzygium aromaticum (cloves)	Aqueous extract	Zhuang et al., 2007[c]

[a]Wu CY, Jan JT, Ma SH, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci U S A 2004;101:10012–10017; [b]Kim HY, Shin HS, Park H, et al. In vitro inhibition of coronavirus replications by the traditionally used medicinal herbal extracts, *Cimicifuga* rhizoma, *Meliae* cortex, *Coptidis* rhizoma, and *Phellodendron* cortex. J Clin Virol 2008;41:122–128; [c]Zhuang M, Jiang H, Xiao P, et al. The inhibitory effects of medicinal herbs on SARS-CoV entry in vitro [abstr 136]. Antivir Res 2007;74:A82–A83; [d]Zhuang M, Jiang H, Suzuki Y, et al. Procyanidins and butanol extract of *Cinnamomi* cortex inhibit SARS-CoV infection. Antivir Res 2009;82:73–81; [e]Yi L, Li Z, Yuan K, et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J Virol 2004;78:11334–1339. [f]Ref. 17.
SARS, Severe acute respiratory syndrome.

fever, was and is a serious bane in Africa where it is native, although it was spread to South and Central America by the slave trade in the seventeenth century.[21] Famously, yellow fever and malaria were incapacitating and killing so many workers on the Panama Canal that the entire plan looked doomed to fail in 1904, until William Crawford Gorgas, MD (1854–1920 AD), the chief medical officer on the project, finally convinced President Theodore Roosevelt (R) to fund a massive mosquito-control campaign. This dropped the levels of disease so much that it enabled the workers to build the canal. Yellow fever was on the decline after the successful invention of a safe, highly effective vaccine in 1937 by Max Theiler, PM (1899–1972 AD; he was awarded the Nobel prize in medicine for this accomplishment in 1951). Alas, yellow fever has been on the rise since the 1980s, currently infecting upward of 170,000 people and killing 60,000 per year, mostly in Africa.[22,23] Yellow fever has a very high lethality rate (50% in epidemics). Low vaccine coverage and lack of treatments necessitate the need for more effective approaches to yellow fever.

Far less lethal but more widespread emerging and reemerging flaviviruses include dengue, West Nile, and Zika viruses.

Dengue emerged as a global disease after World War II and now causes hundreds of millions of infections worldwide each year.[24,25] Many cases are asymptomatic, but dengue can cause both mild-to-severe flulike illness and, rarely, a fairly lethal hemorrhagic fever. A new partially effective vaccine against dengue was approved in Mexico, the Philippines, and Brazil as of early 2016, but remains commercially unavailable.[26]

West Nile virus infection generally is also either asymptomatic or can cause a flulike illness. In 1% of patients (more in patients who are immunocompromised), meningitis, encephalitis, or a poliolike paralytic illness secondary to spinal-cord inflammation occur. West Nile virus is transmitted by *Culex* mosquitoes across North America. It emerged here starting in 1999.[27]

The Zika virus exploded onto the scene in late 2015 when a massive epidemic occurred throughout tropical America (this virus originated in central Africa, having first been identified in Uganda in 1947). Like dengue and West Nile, this virus mostly seems to cause asymptomatic infections in adults, though it can cause a syndrome very like dengue fever. It has also become clear that Zika can cause birth defects, including microcephaly, if it infects pregnant women, and might cause Guillain-Barré syndrome in some unlucky victims.[28] Zika virus is also transmitted sexually. It appears to be spread by *Aedes albopictus* mosquitoes, which range widely in temperate North America, setting the stage for this infection emerging in a wider region of the United States and perhaps even Canada. Note that dengue has also been shown to infect *A. albopictus*.[29]

The history of the emergence of epidemics of most flavivirus-induced diseases is tightly interwoven with the history of the *A. aegypti* mosquito. After 1492, this mosquito was introduced from Africa into the Americas, where it adapted quickly—as it has in all tropical and subtropical areas—to human settlements (as females absolutely require human blood meals, and the mosquitoes vastly prefer laying eggs in artificial containers such as water cisterns).[30] Once the connection between mosquitoes and these infections was made (in the early 1900s, including when workers were digging the Panama Canal, as noted earlier), massive efforts were taken to eradicate *A. aegypti*, including covering water containers and clearing swampland near urban areas. Eventually, pesticides, notably dichlorodiphenyltrichloroethane (DDT), were invented and used extensively. This was massively effective, and by 1970, *A. aegypti* was on the verge of being eliminated.

Unfortunately, the huge success of the campaign against this mosquito faltered when the rates of the diseases it transmitted fell so low that the funding to maintain eradication efforts could not be justified. Additionally, the adverse effects of DDT became clear. The result was a massive reinfestation of the Americas starting in the 1980s to the point today that *A. aegypti* is more widespread than ever. This has allowed for rapid introduction and spread of flaviviruses from Africa into the Americas in modern times. Global warming is likely also extending the range in which this mosquito can thrive.[31]

Treating and Preventing Flavivirus Infections

The only clinical trials of any natural product that could be identified for any flavivirus infection involved *Carica papaya* (papaya) leaves.[32] The most rigorous was an open-label randomized trial involving 228 Malaysian patients with serologically confirmed dengue. The patients were all treated with standard of care, and some also received the juice of 50 g of organic papaya leaf once daily after breakfast for 3 days.[33] Platelet counts rose significantly more in the papaya group, compared to controls, an important sign that the treatment may prevent the dreaded hemorrhagic complications of dengue. No other outcomes were assessed or reported. A much weaker clinical trial of 80 Indonesian patients with clinical dengue fever (not serologically confirmed) randomized them to standard of care or the same with added ethanolic papaya leaf extract in capsules.[34] Platelet counts rose faster in the papaya leaf group, resulting in shorter hospital stays.

One case study showed benefit from papaya leaf in a man with severe dengue fever, although the cause of this fever was not confirmed serologically.[35] He was given 25 mL of crudely juiced papaya leaf mixed with sucrose and water twice daily, after which his symptoms were reduced and his laboratory results improved significantly (his platelet count rose and his WBC count fell). A second case study showed that 150 mL of juiced papaya leaf mixed with sweet fruit juice once per day significantly raised the platelet count of a young man with serologically confirmed dengue fever.[36] A series of 12 cases (although only 6 were serologically confirmed to be dengue infection) in Sri Lanka showed a significant rise in serum platelet counts with use of an unknown dose of a papaya leaf extract twice daily.[37] Further rigorous trials of this promising treatment are needed urgently. However, the ready availability of this highly sustainable medicine, its safety, and preliminary evidence cited here all suggest this should be used in treating dengue patients until, and unless, better options are proven to exist.

Glycyrrhizin is potentially important for treating flavivirus infections as well as coronavirus infections as discussed earlier. In vitro, glycyrrhizin was active against Japanese encephalitis virus, a flavivirus closely related to West Nile virus.[38] Glycyrrhizin also inhibited replication of dengue and yellow fever virus (among other flaviviruses) in vitro, albeit at relatively high concentrations.[39] The effective concentrations were not cytotoxic to healthy cells tested.

Aloysia citriodora (lemon verbena), formerly known as *Lippia citriodora*, is a member of the Verbenaceae family and native to South America. *Lippia alba* (bushy matgrass, *hierba negra*) is a close relative found as far north as Texas and down into South America. The volatile oils of these two cousins were active for inhibiting adsorption of yellow fever virus in vitro at relatively low concentrations.[40] Both oils also inhibited viral replication even after adsorption into host cells. Citral, which is a mixture of geranial (*E*-citral or citral A) and neral (*Z*-citral or citral B) is present in moderate concentrations in lemon verbena oil and was a significant contributor to the anti–yellow fever virus effects. Other even richer sources of citral include *Backhousia citriodora* (lemon myrtle) in the Myrtaceae family and native to Australia; *Litsea cubeba* (*may chang, bì chéng qié*) in the Lauraceae family and native to Indonesia, China, and Taiwan; *Cymbopogon citratus* (lemongrass) in the Poaceae family and native to Southeast Asia; and *Ocimum gratissimum* (clove basil) in the Lamiaceae family and native to Africa, Madagascar, and South Asia.

These herbs, their volatile oils, and citral have repeatedly shown antiviral actions against many other types of viruses in vitro.[41–44] However, an in vitro study showed that a methanol extract of lemongrass was minimally active against dengue (the volatile oil and its components were not studied).[45] Lemon verbena and especially bushy matgrass volatile oils were active against dengue, with a half maxium inhibitory concentration (IC_{50}) as low as 0.4 mcg/mL for bushy matgrass.[46] Bushy matgrass, *Origanum vulgare* (oregano) leaf volatile oil, and *Artemisia vulgaris* (mugwort) leaf volatile oil were also all actively virucidal against yellow fever in vitro.[47] Further research is needed on all of these herbs and their effects on flaviviruses in humans.

Flavonoids, and particular flavonols, have repeatedly produced activity against dengue in vitro. In one study, the ubiquitous flavonol quercetin was very active for inhibiting dengue virus type 2 (there are five known serotypes of this virus, all of which cause disease).[48] Its IC_{50} was 35.7 mcg/mL in the model system used. The flavonol fisetin actively inhibited dengue type 2 replication with an IC_{50} of 55 mcg/mL in vitro; naringenin and rutin (which is the glycoside form of quercetin) were not active in this study.[49] Inhibition of dengue's NS2B-NS3 protease appears to play an important role in quercetin and other flavonoids' (myricetin, also a flavonol, and agathisflavone, a biflavone) ability to inhibit dengue replication postadsorption.[50]

Baicalein is a flavone found in the roots of the important medicinal plant *Scutellaria baicalensis* (Baikal skullcap, *huáng qín*) in the Lamiaceae family. In vitro, baicalein was an extremely potent inhibitor of dengue type 2 with an IC_{50} of 6.46 mcg/mL in one model system.[51] The glycoside, baicalin, also blocked both adsorption of dengue to host cells and was virucidal against it at low concentrations (IC_{50}: 8.74 mcg/mL as a virucidal).[52] An aqueous extract of Baikal skullcap inhibited adsorption and replication of the main four serotypes of dengue (1–4) in vitro.[53] The gut flora contribute to the complex pharmacokinetics of baicalin and baicalein when Baikal skullcap is administered and may help determine if this herb would be effective in particular patients or not.[54] Baikal skullcap and its constituents (even in quite high doses) are safe and, based on in vitro work, are extremely good candidates for clinical research to determine if they would help patients who have dengue.[55]

Many other herbs have shown anti-dengue activity. These are reviewed in Table 4. Whether or not these will be active in humans is unknown, and clinical trials are being conducted.

West Nile virus has not been the subject of as much research as dengue, but there are still some data suggesting that natural products may be helpful in the fight against infection by this organism. Palmatine, an isoquinoline alkaloid isolated from *Coptis chinensis* (goldthread, *huáng lián*), inhibited West Nile by inhibiting its NS2B-NS3 protease in vitro.[56] Palmatine was also active against yellow fever and dengue viruses in this model system. Palmatine and related isoquinoline alkaloids such as berberine have produced antimicrobial effects in many studies against an array of pathogens.[57] Further research is warranted.

Daucus carota ssp. *maritimus* (wild carrot) seed extract strongly inhibited the RNA polymerases of West Nile and dengue viruses (as well as hepatitis C) in vitro in one study.[58] No follow-up research has been done, and wild carrot is not a well-established antiviral, but this novel therapy with a simple and safe medicine (though it can be photosensitizing in large quantities in susceptible people) is worth pursuing to determine if it is effective.

Zika virus is so new that no research on herbal therapies has been conducted to fight it. Given that it is in the same group as the dengue, yellow fever, and West Nile viruses, it makes the most sense to start using agents that have already shown activity against these viruses when searching for herbal agents that might help patients who develop Zika infection.

Alphavirus: Chikungunya

The alphavirus known as chikungunya appears to have originated in East Africa, and was officially described for the first time in 1955. The name derives from the Makonde language and means roughly "that which bends up," referring apparently to people's distorted postures as a result of the severe arthralgia that sometimes accompanies the infection. It was dormant for a while after the 1960s but reemerged with a vengeance in 2004, with large outbreaks across Asia, Africa, and the Americas.[59] Chikungunya, like flaviviruses, is spread principally by *A. aegypti* but also by *A. albopictus*, raising concern that this virus may spread further into Europe and

Table 4. Miscellaneous Anti-Dengue Herbs in Preclinical Research

Herb or constituent	Extract	Reference
Andrographis paniculata (kalmegh) leaf	Methanol extract (note: also kills and repels adult *A. aegypti* mosquitoes[a])	Tang et al., 2012[b]
Azadirachta indica (neem) leaf	Aqueous extract (also effective in infected mice after intracerebral injection)	Parida et al., 2001[c]
Chondrus crispus (Irish "moss"), carrageenan	Isolated compound	Talarico & Damonte, 2007[d]; Talarico et al., 2011[e]
Cyanthillium cinereum = *Vernonia cinerea* (little ironweed) leaf	Methanol extract	Rothan et al., 2014[f]
Eleagnus rhamnoides = *Hippophae rhamnoides* (sea buckthorn) leaf	Ethanol extract (more effective than ribavirin)	Jain et al., 2008[g]
Houttuynia cordata (*houttuynia, yú xīng cǎo*) leaf; hyperoside	Aqueous and ethanol extracts	Klawikkan et al., 2011[h]; Leardkamolkarn et al., 2012[i]
Lanatoside C from *Digitalis lanata* (woolly foxglove)	Cardiac glycoside; also active against chikungunya and other (+)ssRNA viruses	Cheung et al., 2014[j]
Lantana grisebachii leaf	Volatile oil (also antiherpetic)	García et al., 2010[k]
Larrea tridentata (creosote bush) aerial parts	Nordihydroguaiaretic acid	Soto-Acosta et al., 2014[l]
Momordica charantia (bitter melon) fruit	Methanol extract	Tang et al., 2012[b]
Quercus lusticanica (dyer's oak) seed	Unknown extract	Muliawan et al., 2006[m]
Senna alexandrina (senna) leaf	Ethanol and methanol extracts	Rothan et al., 2014[f]
Zingiber officinale (ginger) rhizome	Methanol extract	Sharma et al., 2015[n]
Zostera marina (eelgrass), zosteric acid	Isolated compound	Rees et al., 2008[o]

[a]Govindarajan M, Sivakumar R. Adulticidal and repellent properties of indigenous plant extracts against *Culex quinquefasciatus* and *Aedes aegypti* (Diptera: Culicidae). Parasitol Res 2012;110:1607–1620; [b]Ref. 45; [c]Parida MM, Upadhyay C, Pandya G, Jana AM. Inhibitory potential of neem (*Azadirachta indica* Juss) leaves on dengue virus type-2 replication. J Ethnopharmacol 2002;79:273–278; [d]Talarico LB, Damonte EB. Interference in dengue virus adsorption and uncoating by carrageenans. Virology 2007;363:473–485; [e]Talarico LB, Noseda MD, Ducatti DR, et al. Differential inhibition of dengue virus infection in mammalian and mosquito cells by iota-carrageenan. J Gen Virol 2011;92(pt6):1332–1342; [f]Rothan HA, Zulqarnain M, Ammar YA, et al. Screening of antiviral activities in medicinal plants extracts against dengue virus using dengue NS2B-NS3 protease assay. Trop Biomed 2014;31:286–296; [g]Jain M, Ganju L, Katiyal A, et al. Effect of *Hippophae rhamnoides* leaf extract against dengue virus infection in human blood–derived macrophages. Phytomedicine 2008;15:793–799; [h]Klawikkan N, Nukoolkarn V, Jirakanjanakir N, et al. Effect of Thai medicinal plant extracts against dengue virus in vitro. Mahidol Univ J Pharm Sci 2011;38:13–18; [i]Leardkamolkarn V, Sirigulpanit W, Phurimsak C, et al. The inhibitory actions of *Houttuynia cordata* aqueous extract on dengue virus and dengue-infected cells. J Food Biochem 2012;36:86–92; [j]Cheung YY, Chen KC, Chen HX, et al. Antiviral activity of lanatoside C against dengue virus infection. Antivir Res 2014;111:93–99; [k]García CC, Acosta EG, Carro AC, et al. Virucidal activity and chemical composition of essential oils from aromatic plants of central west Argentina. Nat Prod Commun 2010;5:1307–1310; [l]Soto-Acosta R, Bautista-Carbajal P, Syed GH, et al. Nordihydroguaiaretic acid (NDGA) inhibits replication and viral morphogenesis of dengue virus. Antiviral Res 2014;109:132–140; [m]Muliawan SY, Kit LS, Devi S, et al. Inhibitory potential of *Quercus lusitanica* extract on dengue virus type 2 replication. Southeast Asian J Trop Med Public Health 2006;37:132–135; [n]Sharma BK, Klinzing DC, Ramos JD. Modulatory activities of *Zingiber officinale* Roscoe methanol extract on the expression and activity of MMPs and TIMPs on dengue virus infected cells. Asian Pac J Trop Dis 2015;5(suppl1):S19–S26; [o]Rees CR, Costin JM, Fink RC, et al. In vitro inhibition of dengue virus entry by *p*-sulfoxy-cinnamic acid and structurally related combinatorial chemistries. Antiviral Res 2008;80:135–142.

North America. Infection causes symptoms in 75%–97% of people, including fever, arthralgia without visible joint swelling, rash, and other flulike symptoms that are often severe. A chronic syndrome of arthralgias may occur after clearance of the acute illness, which can last for months to years.[60] Mortality is low from chikungunya, with infants, the elderly, and patients with compromising illnesses having the most apparent deaths.

An increasing number of natural products are showing promise as inhibitors of chikungunya virus. An ethanol extract of *Cynodon dactylon* (Bermuda grass) aerial parts was found to inhibit chikungunya primarily because of the flavones luteolin and apigenin.[61] Bermuda grass is actually native to the Middle East and is quite an invasive species in many other areas. Luteolin was already noted above (in Table 3) as having activity against SARS-CoV. This flavone was also shown recently to both inhibit replication and destroy Japanese encephalitis virus, another flavivirus.[62] The flavone is also active against a range of other viruses, including enteroviruses, coxsackieviruses, and hepatitis B.[63,64] Apigenin also inhibits enteroviruses and foot-and-mouth disease virus.[65,66] Luteolin also inhibited virus-induced inflammation in vitro.[67] Clearly, luteolin should be assessed as a therapy for emerging viral infections.

Several species of *Euphorbia* inhibited chikungunya virus in vitro, probably due primarily to the diterpenoids in the extract.[68] *Euphorbia amygdaloides* ssp. *semiperfoliata* diterpenoids inhibited chikungunya and HIV in vitro.[69] *E. chamaesyce* (prostrate spurge) has been shown to inhibit Epstein–Barr virus.[70] *E. humifusa* (*di jin*) inhibits influenza viruses, particularly through a hydrolyzable tannin from this herb.[71] *Euphorbia tirucalli* (firestick plant), particularly its diterpenoids, inhibits HIV replication in vitro.[72] This diverse genus is obviously another strong candidate for development as an anti-chikungunya virus therapy.

Berberine, an isoquinoline alkaloid in several medicinal plants, such as *Mahonia aquifolium* (Oregon grape) and *Hydrastis canadensis* (goldenseal), is commonly used to treat a range of infectious diseases. Berberine inhibited chikungunya and related alphaviruses (Semliki Forest and Sindbis virus) in vitro.[73] As already noted in the discussion of the closely related alkaloid palmatine used to address flaviviruses, berberine is a broad-acting antiviral.[74–76] Human clinical trials on other infectious diseases and many other conditions have proven that berberine is safe and effective.[77–80] It should be studied for treatment of chikungunya infection.

Other natural products have also been reported to inhibit chikungunya, and they are listed in Table 5. Many of these represent intriguing possibilities for limiting the threat of chikungunya. Some are from native, local plants where chikungunya is currently the biggest problem, and others are from outside these areas, but well-developed clinically for other uses so they are known to be safe (such as curcumin, epigallocatechin gallate, andrographolide, and silymarin). These compounds, extracts, and their combinations are priorities for further testing to determine if they can help people infected with or at risk of infection with chikungunya.

Unfortunately, the recently greatly magnified threat of Ebola virus exploded across West Africa from its more typical home in central Africa. The greatly feared hemorrhagic fever caused by Ebola has extremely high mortality. Fruit bats are now known to serve as a highly mobile reservoir of infection and very likely served to spread it to this new area of Africa.[81] Ebola is now known to remain in various compartments in the bodies of survivors far longer than was previously known, which is particularly a matter of concern as it appears to linger in the testicles and thus could be sexually transmissible.[82]

There has been very little research on herbal approaches to Ebola virus infection. One recent study found that an aqueous extract of *Prunella vulgaris* (heal-all) inhibited entry of Ebola into multiple cells types in vitro.[83] Heal-all is an underutilized antimicrobial from traditional herbal medicine systems across Eurasia previously shown to also inhibit a range of other viruses including influenza, HIV, and herpes simplex.[84–86] It has immune and inflammation-modulating effects that are also important in helping calm viral infection syndromes.[87]

Stephania tetrandra (stephania, *hàn fáng jĭ*) root contains the intriguing *bis*-benzylisoquinoline alkaloid tetrandrine well-documented to be a calcium channel blocker among many other actions.[88] Ebola apparently enters its main cellular targets, macrophages, partly through endosomal calcium channels called two-pore channels. Tetrandrine was highly effective at blocking these channels and thus limiting Ebola entry into macrophages in vitro.[89] It is safe based on clinical trials in extremely compromised patients with silicosis (which also showed some benefits in these patients).[90]

Heal-all, stephania, and tetrandrine are ripe for further development to treat Ebola infection. Other reports of the potential effects of herbs and their constituents on Ebola are eagerly awaited.

Table 5. Other Natural Products That Inhibit Chikungunya Preclinically

Herb	Extract or constituent	Reference
Curcuma longa (turmeric) rhizome	Curcumin	von Rhein et al., 2016[b]
Boswellia serrata (frankincense) gum	Gum resin	von Rhein et al., 2016[b]
Camellia sinensis (green tea) leaf	Epigallocatechin gallate	Weber et al., 2015[c]
Trigonostemon howii (*chang xu san bao mu*)	Diterpenoids	Bourjot et al., 2012[d]
Trigonostemon cherrieri bark[a]	Diterpenoids	Allard et al., 2012[e,f]
Flacourtia indica (ramontchi, governor's plum) bark	Crude extracts	Bourjot et al., 2012[g]
Anacolosa pervilleana leaf	Ethyl acetate extract, terpenoids	Bourjot et al., 2012[h]
Croton mauritianus (woodscent tea)	Diterpenoids	Corlay et al., 2014[i]
Andrographis paniculata (kalmegh) leaf	Andrographolide	Wintachai et al., 2015[j]
Silybum marianum (milkthistle) seed	Silymarin	Lani et al., 2015[k]
Cephalotaxus harringtonii (Japanese plum yew) seed	Harringtonine	Kaur et al., 2013[l]

[a]This is a critically endangered species according to the International Union for the Conservation of Nature (Visit: www.iucnredlist.org/details/summary/35025/0).
[b]von Rhein C, Weidner T, Henß L, et al. Curcumin and *Boswellia serrata* gum resin extract inhibit chikungunya and vesicular stomatitis virus infections in vitro. Antiviral Res 2016;125:51–57; [c]Weber C, Sliva K, von Rhein C, et al. The green tea catechin, epigallocatechin gallate inhibits chikungunya virus infection. Antiviral Res 2015;113:1–3; [d]Bourjot M, Delang L, Nguyen VH, et al. Prostratin and 12-*O*-tetradecanoylphorbol 13-acetate are potent and selective inhibitors of chikungunya virus replication. J Nat Prod 2012;75:2183–2187; [e]Allard PM, Leyssen P, Martin MT, et al. Antiviral chlorinated daphnane diterpenoid orthoesters from the bark and wood of *Trigonostemon cherrieri*. Phytochemistry 2012;84:160–168; [f]Allard PM, Martin MT, Dau ME, et al. Trigocherrin A, the first natural chlorinated daphnane diterpene orthoester from *Trigonostemon cherrieri*. Org Lett 2012;14:342–345; [g]Bourjot M, Leyssen P, Eydoux C, et al. Flacourtosides A–F, phenolic glycosides isolated from *Flacourtia ramontchi*. J Nat Prod 2012;75:752–758; [h]Bourjot M, Leyssen P, Eydoux C, et al. Chemical constituents of *Anacolosa pervilleana* and their antiviral activities. Fitoterapia 2012;83:1076–1080; [i]Corlay N, Delang L, Girard-Valenciennes E, et al. Tigliane diterpenes from *Croton mauritianus* as inhibitors of chikungunya virus replication. Fitoterapia 2014;97:87–91; [j]Wintachai P, Kaur P, Lee RC, et al. Activity of andrographolide against chikungunya virus infection. Sci Rep 2015;5:14179; [k]Lani R, Hassandarvish P, Chiam CW, et al. Antiviral activity of silymarin against chikungunya virus. Sci Rep 2015;5:11421; [l]Kaur P, Thiruchelvan M, Lee RC, et al. Inhibition of chikungunya virus replication by harringtonine, a novel antiviral that suppresses viral protein expression. Antimicrob Agents Chemother 2013;57:155–167.

Conclusion

Emerging viral infections are an ongoing major threat to health around the world. Tools to prevent and treat such infections are currently limited. The time scale to develop effective vaccines and drug therapies in rapidly expanding epidemics is too long to be of much use in many cases. Natural products potentially offer a much more rapid and safe route to alleviating these plagues effectively. An abundance of research suggests both well-characterized and less well-known medicinal plants from around the world, both crude extracts and isolated constituents from these plants, are very promising as treatment for recently or currently emerging coronavirus, flavivirus, and alphavirus infections. The few clinical studies that have been done tend to support preclinical research and suggest more resources should be diverted to determining if other promising leads will pan out clinically. It is hoped that this compilation will help researchers and clinicians better address these devastating infections. ■

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Eric Yarnell, ND, RH (AHG), is chief medical officer of Northwest Naturopathic Urology, in Seattle, Washington, and is a faculty member at Bastyr University in Kenmore, Washington.
