

REVIEW

A status report with critical analysis of research trends in exploring medicinal plants as antiviral: Let us dig into the history to predict the future

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The review article serves as a mini directory of medicinal plants (662 medicinal plants have been identified) that have been investigated for antiviral property between 2015 and 2019. Data have been extracted from Scopus using specific keywords followed by manual sorting to avoid any duplication. Critical analyses of handpicked data have been presented. Mapping of medicinal plants, followed by critical analysis on the families and plant parts investigated in the said tenure, and its correlation with the participating countries and virus types have been critically analyzed. Interceptable role of phytochemicals in impeding viral replication has also been taken note of. Emphasis on India's exploration of various medicinal plants has also been given. Also presents a tutelage, which is likely to revive the interest in natural products for search of potential antivirals. This review is expected to serve as a rich data bank and as a guiding principle for researchers who are planning to explore medicinal plants in search for potential antiviral. It is time that researchers need to revisit their countries' own history of traditional medicine to predict something worthwhile in future.

KEYWORDS

antiviral, COVID-19, medicinal plant, SCOPUS

1 | INTRODUCTION

Viral diseases have always been a menace for public health. Considering the havoc of 1918 Spanish Flu, history is on the verge of repeating itself through its second version as COVID-19 pandemic (Ciotti et al., 2020; More et al., 2020). The cases of morbidity and mortality are the highest with viral diseases and the situation even worsens with the fact that the arsenal of antiviral drugs are not rich enough and do not have a wide spectrum with vaccination limited to only a selected viral diseases (Meijer, Jansen, & Molema, 1992). Moreover, the cost of available antivirals is on the higher side with the issue of resistance also cannot be ignored, which makes the situation more grim (Yashaswini, Geetha, & Prashanth, 2019). Migration of people to different countries for jobs, global travel, and urbanization has also been cited as one of the causes for spread of viral diseases (Denaro

et al., 2020). Henceforth, it is the right time to revisit the options available from nature. Nature with its rich diversity of medicinal plants has always come to the rescue of mankind alleviating pain and suffering due to different diseases (Halberstein, 2005). Nevertheless, the current situation of COVID-19 is no different, as traditional Indian and Chinese medicines have shown a positive intervention in the management of COVID-19 (Hussain et al., 2020; Thota, Balan, & Sivaramakrishnan, 2020).

Data mining from Scopus revealed a whopping 489 published reviews in the last 5 years (2015–2019). The Scopus search was carried out with the help of the keywords “antiviral” and “extract.” Careful manual sorting and elimination of duplication revealed that 215 review articles were committed to the involvement of medicinal plants as antiviral. Out of these 135, 29, 37, and 14 review articles were dedicated to exploring the antiviral potential of one particular

plant, isolated pure compounds from plants, plants belonging to a particular family or genus, and cluster of plant species on a particular virus, respectively (Scopus, 2020). Most of these articles are a consolidation of whatever work has been done in the context of antiviral activity highlighting the mechanism and to some extent the chemistry involved.

With so much availability of enriched literature in the scientific domain pertaining to involvement of medicinal plants in antiviral research, some of which are even committed to COVID-19, (Brendler et al., 2020; Denaro et al., 2020; Islam et al., 2020) makes the task even more difficult to justify the need for another review, which will have something new to offer for the readers. Having said this, this review article was strategically designed to present a quantitative data on the available literature, highlighting the involvement of medicinal plants as a safer antiviral option. This review more or less shall serve as a one-stop destination or rather a medicinal plant directory (soft data bank) for those interested in exploring medicinal plants as antiviral. A quantitative consolidation with critical analysis has been presented to map down the research trends pertaining to antiviral and medicinal plants. It is a sincere attempt to dig deep into the history to predict the future.

2 | DATA MINING

The entire data for understanding the research trends pertaining to antiviral and medicinal plants were extracted from Scopus database as per the search parameters listed in Table 1. A 5-year span from 2015 to 2019 was used for data collection followed by critical analysis. Data mining from Scopus offers several advantages when compared to other several scientific databases, which have been very well exemplified by the authors in their previous publications, which are based on similar data mining projects from Scopus followed by critical analysis (Chouhan, Tandey, Sen, Mehta, & Mandal, 2019; Mandal et al., 2018; Mandal & Tandey, 2016). All crude data extracted from Scopus were manually sorted and only those articles that had any relevance with medicinal plants including marine plants were included in the final qualified list of articles. The qualified list was deemed to be consisting of those articles that deal with medicinal plants and antiviral research,

TABLE 1 Details of search parameters used for data mining from Scopus database

Search parameters	Practicable settings
Search term text	<Extract>
Search field type	Article title, abstract, keywords
Data range	2015–2019
Document type	< article>
Subject areas	Pharmacology, Toxicology, Medicine, Chemistry, Agriculture, Biological sciences
Operator used between two search terms	Extract <and> Antiviral

which is the key point of discussion for this review article. Figure 1 indicates the first-hand data extracted from Scopus reflecting the number of publications with the applied keywords year wise and the actual qualified articles year wise after manual sorting. The Pearson coefficient value r was found to be -0.30 , which indicates a negative correlation between the number of publications based on antiviral research actually extracted from Scopus on per year basis and those that were actually found to qualify (had relevance to medicinal plants). In light of the above fact, it can be anticipated that if the number of publications associated with medicinal plants pertaining to antiviral research increases every year, the actual number of relevant articles is likely to decrease. This could be due to the lesser consideration of medicinal plants as being a potential source for antiviral therapy. One of the main reasons for this observation could be lack of trust on plant extracts to be used as potential therapeutic alternative for treatment of various diseases by western countries, such trust issues further gain ground due to the inconsistency being observed with plant extracts because of poor standardization parameters. But the current COVID-19 pandemic has definitely produced sound clinical evidence that herbal crude drugs can play a pivotal role in the treatment and management of viral diseases (Antonio, Wiedemann, & Veiga-Junior, 2020; Wu et al., 2020); having learned that clinical use of certain synthetic drugs during this pandemic situation turned out to be either ineffective or extremely toxic (Kalil, 2020). Another interesting data extraction was carried out from SCOPUS database using “medicinal plant” and “COVID-19” as the keywords. A total of 214 articles were extracted. The criterion for data sorting was that any claim for a particular medicinal plant to be effective in COVID-19 management must be accompanied by scientific evidences such as docking studies or in vitro experiments. Nevertheless, in vitro assay methods need a committed antiviral lab facility and in this unprecedented lockdown situation it is understood that access to lab facility of various Universities and research institutions might have been restricted. So, at least evidences in the form of docking study must be available for qualifying any data. Data in this regard reflect those medicinal plants that may have positive role in COVID-19 management backed up by at least docking studies. A total of 78 medicinal plants were found to qualify as per the criteria established.

3 | CRITICAL ANALYSIS

3.1 | Plant names and family

A total of 510 plants as given below were investigated for their possible antiviral activity. The names of all the plants (from newest to oldest) are mentioned below, which is likely to serve as a gold mine for any natural product researcher (plants marked with * indicate that the particular plant has been scientifically explored for the treatment and management of COVID-19 during this pandemic time).

2019:

Acacia catechu (A), *Acorus calamus*, *Agrimonia pilosa*, *Aleurites moluccana*, *Allium sativa*, *Prunus dulcis* (Almond), *Aloe barbadensis* (Aloe

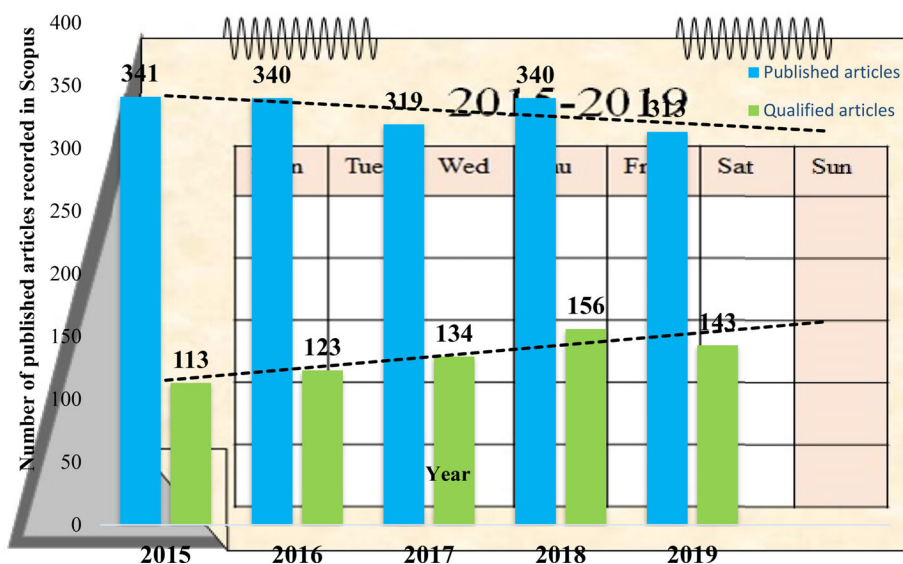


FIGURE 1 Search results depicting publications registered in Scopus. Raw data vs. Filtered data (articles that actually qualified for the purpose of review). Publication database: Scopus, Time span: 2015–2019, Keywords: <antiviral and extract> [Colour figure can be viewed at wileyonlinelibrary.com]

vera), *Ambrosia cumanensis*, *Andrographis paniculata** (India), *Annona squamosa* (India), *Arnebia euchroma*, *Astragalus membranaceus*, *Baphicacanthus cusia*, *Hordeum vulgare* (Barley), *Basilicum polystachyon*, *Bauhinia holophylla*, *Boscia senegalensis*, *Brassica juncea*, *Brennia disticha*, *Brassica oleracea* (Broccoli), *Cananga odorata*, *Carica papaya** (India), *Cassia fistula*, *Cavanillesia platanifolia*, *Ceanothus coeruleus*, *Cedrus deodara* (India), *Cephalotaxus harringtonii*, *Chenopodium ambrosioides*, *Chrysactinia mexicana*, *Chrysobalanus icaco*, *Cimicifuga heracleifolia*, *Cladogynos orientalis*, *Clematis drummondii*, *Clerodendrum trichotomum*, *Commiphora wightii* (India), *Croton malambo*, *Cymbopogon citratus*, *Cynomorium coccineum*, *Cyperus rotundus*, *Dianthus superbus*, *Diospyros inconstans*, *Elaeocarpus tonkinensis*, *Euphorbia pulcherrima*, *Eurycoma longifolia*, *Forsythia suspensa*, *Forsythia viridissima*, *Galla rhois*, *Scutellaria baicalensis**, *Geranium thunbergii**, *Glycosmis pentaphylla* (India), *Graptopetalum paraguayense*, *Camellia sinensis** (Green tea), *Psidium guajava** (Guava), *Citrus limon* (Lemon), *Himatanthus bracteatus*, *Houttuynia cordata*, *Acanthus ilicifolius*, *Inula britannica*, *Jatropha curcas*, *Juglans mollis*, *Juncus maritimus*, *Justicia procumbens*, *Lampranthus coccineus*, *Lilium speciosum*, *Limonium morisianum*, *Lonicera japonica*, *Lophatherum gracile*, *Ephedra sinica* (Ma Huang Tang), *Malephora lutea*, *Malva sylvestris*, *Mammea americana*, *Momordica charantia* (India), *Myristica fatua*, *Nephelium lappaceum*, *Nerium oleander**, *Ocimum tenuiflorum* (India), *Panax ginseng*, *Patallus mollis*, *Pavetta tomentosa* (India), *Persea americana*, *Phoenix dactylifera*, *Phyllanthus urinaria* (India), *Picrorhiza kurroa* (India), *Plantago asiatica*, *Psiloxylon mauritianum*, *Pulchellum cochinchinensis*, *Punica granatum* (India) *Putranjiva roxburghii*, *Radix Isatidis*, *Rapanea melanophloeos*, *Rhinacanthus nasutus*, *Rhododendron latoucheae*, *Ricinus communis*, *Ruprechtia polystachya*, *Ruprechtia salicifolia*, *Salvadora persica*, *Salvia ballotaeflora*, *Salvia texana*, *Sambucus formosana*, *Sarcocornia fruticosa*, *Sarcostemma clausum*, *Selaginella delicatula*, *Silybum marianum*, *Solanum nigrum*, *Glycine max* (Soybean), *Synadenium grantia*, *Tanacetum parthenium*, *Tarenna asiatica* (India), *Terminalia chebula** (India), *Tetrastigma hemsleyanum*, *Persicaria maculosa* (Thumb), *Trichilia hirta*, *Verbascum pterocalycinum*, *Viscum coloratum*.

2018:

Acacia albida, *Acacia nilotic*, *Acacia pennata*, *Acorus tatarinowii*, *Aesculus hippocastanum*, *Ajuga bracteosa*, *Ajuga parviflora*, *Albizia anthelmintica*, *Althaea rosea*, *Anthyllis vulneraria*, *Arachis hypogaea*, *Archidenron pauciflorum*, *Artemisia capillaris*, *Berber islycium*, *Bulbine frutescens*, *Burkea africana*, *Caesalpinia pulcherrima*, *Calea integrifolia*, *Canarium album*, *Casearia coriacea*, *Cassia roxburghii*, *Cassia sieberiana*, *Celastrus hindsii*, *Centaurea aegyptiaca*, *Centaurea alexanderina*, *Centaurea calcitrapa*, *Centaurea glomerata*, *Centaurea pallescens*, *Centipeda minima*, *Cleistocalyx perculatus*, *Clerodendrum glabrum*, *Commelina benghalensis*, *Copaifera reticulata*, *Crataegus azarolus*, *Curcuma domestica*, *Curcuma heyneana*, *Curcuma longa**, *Curcuma xanthorrhiza*, *Cussonia spicata*, *Cynometra cauliflora*, *Datura stramonium*, *Ecklonia arborea*, *Embelia ribes*, *Equisetum arvense*, *Equisetum giganteum*, *Eucalyptus globulus**, *Euphorbia abyssinica*, *Euphorbia antiquorum*, *Euphorbia cooper*, *Euphorbia kansui*, *Euphorbia umbellata*, *Faramea hyacinthina*, *Faramea truncata*, *Guiera senegalensis*, *Humulus lupulus*, *Hypericum scruglii*, *Iris confusa*, *Isodon eriocalyx*, *Juncus compressus*, *Justicia gendarussa*, *Alternanthera brasiliensis* (Kuntze), *Lagerstroemia speciosa* (India), *Lepidium sativum*, *Ligustrum lucidum*, *Lindernia ruellioides*, *Macaranga barteri*, *Mammea harmandii*, *Mangifera indica*, *Melia azedarach*, *Melissa officinalis*, *Monimia rotundifolia*, *Morus alba*, *Moslae herba*, *Nitraria schoberi*, *Nymphaea alba*, *Oroxylum indicum*, *Peganum harmala*, *Phaleria macrocarpa*, *Phyllanthus emblica** (India), *Pistacia atlantica*, *Pittosporum viridiflorum*, *Platycodon grandiflorum*, *Polygonum equisetiforme*, *Poncirus trifoliata*, *Poupartia borbonica*, *Psiadia retusa*, *Psidium guayava*, *Pueraria lobata*, *Retama raetam*, *Rhizoma coptidis*, *Rhodiola rosea*, *Rosmarinus officinalis*, *Rumex vesicarius*, *Salvia plebeia*, *Sanguisorba officinalis*, *Schizonepeta tenuifolia*, *Simira eleiezeriana*, *Simira glaziovii*, *Solanum melongena*, *Sophora flavescens*, *Syzygium aromaticum**, *Tabernaemontana ventricosa*, *Tamarix aphylla*, *Taraxacum officinale*, *Terminalia mulleri*, *Thymus vulgaris*, *Truncatella angustata*, *Urtica dioica*, *Uvaria angolensis*, *Vaccinium macrocarpon*, *Vernonia fimbrillifera*, *Veronica persica*, *Vitex doniana*, *Xylocarpus granatum*, *Zanthoxylum heterophyllum*, *Ziziphus mauritiana*,

2017:

Antidesma bunius (), *Abutilon figarianum*, *Acacia oerfota*, *Ageratina havanensis*, *Alchemilla vilgaris*, *Allium sativum* (), *Alnus japonica*, *Angelica archangelica*, *Arctium lappa*, *Artemisia scoparia*, *Artocarpus altilis*, *Artocarpus camansi*, *Artocarpus heterophyllus*, *Arum palaestinum*, *Aspalathus linearis* (), *Asplenium nidus*, *Azadirachta indica** (), *Ballota macrodonta*, *Bletilla striata*, *Boerhavia diffusa* (), *Crocus graveolens* (), *Colebrookea oppositifolia* (), *Cleitanthus patulus* (), *Calystegia soldanella*, *Camelina sativa*, *Capparis decidua*, *Capsicum annuum*, *Celosia cristata*, *Cinnamomi ramulus*, *Cinnamomum zeylanicum*, *Cistus salvifolius*, *Coccinea grandis*, *Coptidis Rhizoma*, *Corallocarpus epigeus*, *Coriandrum sativum*, *Cornus canadensis*, *Cortex moutan*, *Cynanchum paniculatum*, *Cynometra ramiflora*, *Dasymaschalon rostratum*, *Daucus carota*, *Dichrostachys cinerea*, *Dioscorea bulbifera*, *Elaeocarpus sylvestris*, *Eleutherococcus senticosus*, *Eucalyptus sideroxylon*, *Eupatorium fortune*, *Euphorbia pithyusa*, *Euphorbia semperfoliata*, *Fareamea bahiensis*, *Ficus septica*, *Fridericia formosa*, *Fumaria parviflora*, *Garcinia speciosa*, *Ginkgo biloba*, *Gomphocarpus fruticosus*, *Vitis vinifera** (Grape), *Coffea canephora* (Green coffee), *Gynostemma pentaphyllum*, *Hypericum gaitii* (), *Helichrysum kraussii*, *Hemidesmus indicus*, *Hibiscus sabdariffa*, *Indigofera caerulea*, *Indigofera heterantha* (), *Isatidis Radix*, *Isatis indigotica** , *Ixora undulate*, *Jatropha multifida*, *Kaempferia parviflora*, *Kalanchoe pinnata*, *Laggera pterodonta*, *Laminaria japonica*, *Lasiosphaera fenzi*, *Lobelia chinensis*, *Loranthus micranthus*, *Lysimachia mauritiana*, *Myristica extensa* (), *Mangrove rhizophora* (), *Marcetia taxifolia*, *Pistacia lentiscus* (Mastic gum), *Maytenus gonoclada*, *Meliae fructus*, *Mentha piperita*, *Mentha pulegium*, *Norantea brasiliensis*, *Ostodes katharinae*, *Protium serratum* (), *Paeonia suffruticosa*, *Pinnatifida fructus*, *Pleuropterus multiflorus*, *Polygonum chinense*, *Polygonum cuspidatum*, *Solanum tuberosum* (Potato peels), *Pragmites australis*, *Prunus domestica* (), *Psidium guinense*, *Pulicaria crispa*, *Quercus brantii*, *Rubus ellipticus* (), *Rabdosia japonica*, *Radix Crataegus*, *Raphanus sativus*, *Rhodiola kirilowii*, *Rhoeo discolor*, *Rindera lanata*, *Salvia cryptantha*, *Schinus terebinthifolia*, *Selaginella uncinata*, *Sonneratia paracaseolaris*, *Swertia bimaculata*, *Syzygium jambos*, *Tabernaemontana cymosa*, *Taxillus sutchuenensis*, *Tectona grandis* (), *Terminalia paniculata* (), *Termination chebula*, *Tripterygium wilfordii*, *Uncaria guinanensis*, *Ventilago maderaspatana* (), *Valeriana wallichii* (), *Zingiber officinalis**

2016:

Achyranthes aspera, *Acidum ascorbicum*, *Adansonia digitata* (), *Aglaia andamanica*, *Alhagi maurorum*, *Alternanthera philoxeroides*, *Alternanthera sessilis*, *Angelica tenuissima*, *Anthocleista djalonensis*, *Asystasia gangetica*, *Atractylodis rhizoma**, *Bambusa vulgaris* (Bamboo), *Boswellia serrate**, *Callistemon viminalis*, *Carthamus tinctorius*, *Cassia obtusifolia*, *Cissampelos sympodialis*, *Cistus quadrangularis*, *Cistus incanus*, *Cleistocalyx operculatus*, *Clinacanthus nutans*, *Theobroma cacao* (Cocoa), *Crataegus pinnatifida*, *Croton megalobotrys*, *Cuminum cyminum*, (Cumin) *Cynara cardunculus*, *Dasymaschalon sootepense*, *Dimocarpus longan*, *Duabanga grandiflora*, *Eisenia arborea*, *Eleusine indica*, *Eupatorium perfoliatum* (Boneset), *Euphorbia dendroides*, *Euphorbia erythradenia*, *Euphorbia humifusa*, *Euphorbia spinidens* (), *Fagara zanthoxyloides**, *Ficus religiosa*, *Flos chrysanthemi indici*, *Flueggea virosa*,

Forsythia suspense, *Fructus lycii*, *Galla chinensis*, *Garcinia oblongifolia*, *Haloxylon recurvum*, *Haloxylon salicornicum*, *Hoodia gordonii*, *Hypericum japonicum*, *Ilex asprella*, *Ipomoea aquatica*, *Kalanchoe daigremontiana*, *Khaya grandifoliola*, *Leonurus japonicas*, *Glycyrrhiza glabra** (Licorice), *Ligustrum purpurascens*, *Limonium densiflorum*, *Litchi chinensis** (Lychee), *Metasequoia glyptostroboides*, *Morinda citrifolia*, *Moringa oleifera**, *Myracrodruon urundeuva*, *Paeonia delavayi*, *Panicum antidotale*, *Persicaria odorata*, *Phellodendron amurense*, *Pinus kesiya*, *Platyclusus orientalis*, *Plumbago indica* (), *Prunella vulgaris*, *Polygonum multiflorum*, *Radix astragali**, *Rheum officinale*, *Rheum palmatum*, *Rubia cordifolia*, *Rubus chingii*, *Rubus coreanus**, *Scabiosa tschilliensis*, *Salacia reticulata*, *Salsola baryosma*, *Sasa senanensis*, *Scabiosa comosa*, *Schinus molle*, *Sporobolus icolados*, *Strychnos pseudoquina*, *Swertia patens*, *Talinum fruticosum*, *Taxodium distichum*, *Terminalia sericea*, *Thymus daenensis*, *Thymus nummularis*, *Vaccinium corymbosum*, *Zanthoxylum piperitum*,

2015:

Acacia mellifera, *Achillia fragrantissima*, *Achyrocline bogotensis*, *Adenantha pavonina*, *Albizia procera*, *Aleurites fordii*, *Aloe arborescens*, *Aspidistra elatior*, *Berberis holstii*, *Bombax malabaricum*, *Bursera simaruba*, *Caesalpinia ferrea*, *Calluna vulgaris*, *Cassia grandis*, *Chloroxylon swietenia* (), *Cinnamomum cassia*, *Citrus reticulata*, *Cynodon dactylon*, *Daphne gnidium*, *Dimorphandra gardneriana*, *Diotacanthus albiflorus* (), *Dracocephalum heterophyllum*, *Eisenia bicyclis*, *Epimedium koreanum*, *Eucalyptus camaldulensis*, *Eucalyptus torelliana*, *Euphorbia milii*, *Hydrocotyle sibthorpioides*, *Hypericum roeperianum*, *Knoxia valerianoides*, *Magnolia grandiflora* (Magnolia tree), *Pinus pinaster*, *Mercurialis annua*, *Vigna radiata* (MBS), *Nepeta nuda*, *Nitraria retusa*, *Paris polyphylla*, *Paulownia tomentosa*, *Pedilanthus tithymaloides* (), *Phragmanthera capitata*, *Phyllanthus niruri**, *Phyllanthus urinaria*, *Pinus massoniana*, *Portulaca oleracea*, *Pteris henryi*, *Radix trichosanthis*, *Sambucus nigra*, *Sasa quelpaertensis*, *Saururus chinensis*, *Elaeagnus rhamnoides* (Sea buckthorn), *Sophora tonkinensis*, *Stellera chamaejasme*, *Strychnos minor* (), *Strychnos nux-vomica** (), *Swertia Chirayita*, *Swertia mussoitii*, *Teucrium chamaedrys*, *Teucrium pseudochamaepitys*, *Thymus capitatus*, *Tomato pomace*, *Trachyspermum ammi*, *Trichilia dregeana*, *Ulmus pravifolia*, *Xylocarpus moluccensis*, [*Ephedra sinica*, *Pinellia ternate*, *Zingiber officinale*, *Tussilago farfara*, *Aster tataricus*, *Ziziphus jujube*, *Belamcanda chinensis*, *Asarum sieboldii*, and *Schisandra chinensis*] (*Yakammaoto*), *Zymolytic grain*.

These plants are spread across different countries as indicated in Figure 2. Among the top four countries that have investigated the maximum number of medicinal plants (2015–2019); barring Egypt all the other four countries are actually Asian countries. Out of these 510 plants, 21.9% of plants (highest) were investigated by Chinese researchers and can be anticipated that these plants originated from China as it is likely that investigators would prefer exploring the biodiversity and the medicinal flora of their own country. Next to China, 11.1% of plants were investigated by Egypt, followed by 10.9% plants (indicated by Indian national flag within parenthesis in the above list) being investigated by Indian researchers, and 6.66% plants by South Korea. However, apart from *Phyllanthus* species no other plants were found common between Indian and China. On the other hand, no

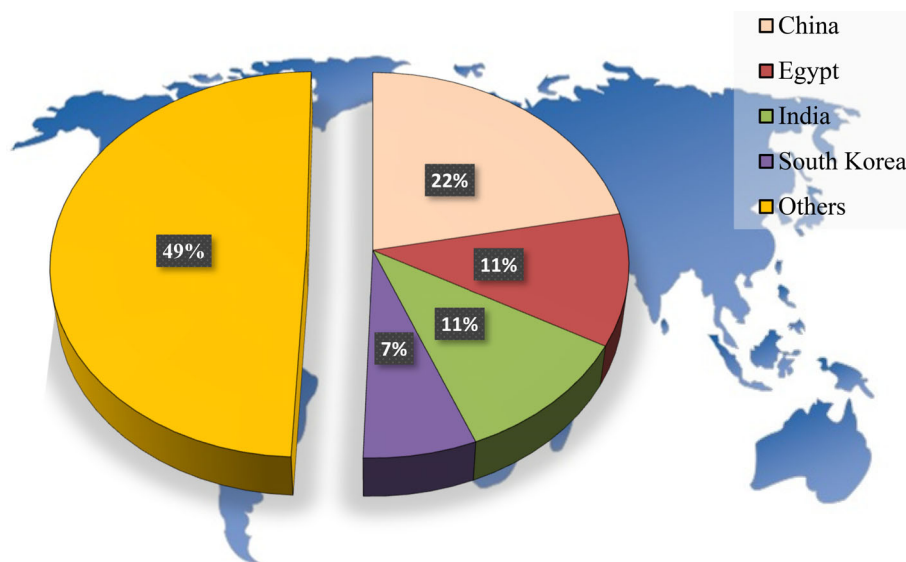


FIGURE 2 Rankings of top five countries that have investigated the most number of plants out of the total 662 plants that have been investigated between 2015 and 2019 [Colour figure can be viewed at wileyonlinelibrary.com]

plants of Egypt and South Korea were found common with that of India. These four countries together constituted 50.5% of the total plants that have been screened for antiviral activity in the said tenure (2015–2019). There is no element of surprise involved because these four countries have a rich history of traditional knowledge. Traditional Chinese Medicine, Egyptian Ancient Medicine, Ayurveda, and Korean Traditional Medicine are widely popular due to their richness in medicinal plants (Kang, Komakech, Karigar, & Saqib, 2017). Having such a rich traditional history provides a perfect research platform to investigate medicinal plants and provide scientific validation to the claims associated with the practice of traditional knowledge and that is what exactly is reflected from the data presented.

These 510 plants were spread across 305 different families. The families of all plants that were studied for investigation of antiviral activity in the tenure between 2015 and 2019 were mapped down. The three most commonly used families were found to be Asteraceae, Fabaceae, and Lamiaceae, which were found to provide a contribution of 11.1, 13.4, and 12.4%, respectively. Asteraceae family in general consists of glycoside, flavonoids, tannins, mucilage, carbohydrate, sabinene, β -pinene, myrcene, limonene, δ -cadinene, nerolidol, viridifloral, α -muurolol and α -cadinol, α - and β -pinene, myrcene, limonene, bicyclogermacrene, δ cadinene, caryophyllene oxide, cubenol and α -cadinol, α -thujene, α and β -pinene, sabinene, myrcene, limonene, and terpinen-4-ol. Some specific new bioactive compounds to mention are chlordanediterpenoids, gaudichanolides A and B, cynaroside I and cosmosiin II, arctigenin, and tacheloside (Koc, Isgor, Isgor, Shomali Moghaddam, & Yildirim, 2015).

Fabaceae can produce more nitrogen-containing secondary metabolites (especially, NPAA, glucosinolates, amines, and alkaloids) than other non-nitrogen fixing plants. Alkaloids and amines are mostly present in plants belonging to **Fabaceae** families (Arceusz, Radecka, & Wesolowski, 2010). Quinolizidine alkaloids such as Sparteine, lupanine, anagrine, cytosine, matrine, lupinine, and Pyrrolizidine alkaloids such as Monocrotaline, senecionine, and Indolizidine alkaloids such as Swainsonine, castanospermine, and Piperidine alkaloids such

as Ammodendrine, 2-Piperidine carboxylic acid, 4-hydroxy-2-piperidine carboxylic acid, and Pyridine alkaloids such as Trigonelline, Indole alkaloids, namely Physostigmine, Erythrina alkaloids, namely Erysodine, erysopine, erythraline, Simple isoquinoline alkaloids, namely Salsoline, salsolidine, and Imidazole alkaloids, such as Cynodine, cynometriner, and Polyamines such as Spermine, spermidine, and Phenylethylamines such as N-Methyl phenylethylamine, Cyanogenic glucosides, namely Prunasin, linamarin, lotaustraline, and proacacipetalin, Simple phenols like Vanillin, syringic acid, ferulic acid, gentisic acid, gallic acid, p-hydroxybenzaldehyde, Flavonoids like Quercetin, kaempferol, Isoflavones like Genistein, daidzein, formononetin, Pterocarpans such as Maackiain, glycinol, acanthocarpan, cristacarpin, glyceollin, medicarpin, phaseollin, pisatin, variabilin, Rotenoids such as Rotenone, Catechins like Catechin, epicatechin, catechin gallate, epigallocatechin gallate, Anthocyanins like Delphinidin, Peonidin, Cyanidin, Coumarins and furano coumarin such as Umbelliferone, scopolin, psoralen, bergapten, xanthotoxin and Monoterpenes like Linalool, citronellal, and limonene are mostly found in Fabaceae family. Antiviral properties obviously cannot be attributed to a single phytoconstituent but it is more likely that various bioactive compounds acting in tandem is responsible for the antiviral action.

Lamiaceae (Labiatae) family is one of the most widely distributed medicinal plants around the globe with diversified uses such as medicinal, flavoring, perfumery, culinary, and ornamental purposes. Traditionally plants of Lamiaceae have been used in various indigenous systems of medicines and also as functional foods (Carović-Stanko et al., 2016; Uritu et al., 2018). Plants belonging to this family are rich in terpenes, alkaloids, phenols, phenolic acids, tannins, steroids, and flavonoids. Some of the extensively reported and scientifically validated traditional uses of this particular family are antioxidant, anticancer, antipyretic, anti-inflammatory, anesthetic, hepatoprotective, antidiabetic, smooth muscle relaxant, antitumor, treatment of wound healing, headache, pains, chronic rheumatism, sedative, and gastrointestinal disorders (Nayeem & Mehta, 2015). Volatile and nonvolatile principles are the major class of bioactive compounds present in the

plants of Lamiaceae family (Fazal & Islam, 2019). Some specific phytoconstituents, which have been extensively isolated from plants of this family, are sterols, sideroxol, β -bisabolene, rosmarinic acid, ursolic acid, menthol, thymol, and carvacrol. The genus *Clerodendrum* L. belonging to the family Lamiaceae is very widely distributed and includes over 450 species with a large array of traditional uses as mentioned above and galaxy of bioactive compounds (Nayeem & Mehta, 2015). Lamiaceae family has been extensively reviewed for its role in pain therapy (Uritu et al., 2018). Plants such as *Mentha*, *Ocimum*, *Rosmarinus*, *Salvia*, *Thymus*, and *Lavandula* have been found to be extensively used in pain therapy as per published reports (Uritu et al., 2018). Some of the notable volatile principles from this family, which have been found to play a major role in pain therapy, antimicrobial activity, and several other biological properties, are thymol, geraniol, thujanol, linalool, carvacrol, borneol, eugenol, myrcene, β -phellandrene, β -pinene, germacrene, α -thujone, chavicol, menthol, lavandulol, etc. (Uritu et al., 2018).

A list of COVID-19 dedicated medicinal plants based on SCOPUS data extraction as explained above are presented below, which can be considered as a data bank for future scientific exploration in search of possible antiviral leads with special emphasis to COVID-19.

Acacia Senegal, *Ancistrocladus tanzaniensis*, *Andrographis paniculate*, *Atractylodis macrocephalae*, *Atractylodis rhizoma*, *Azadirachta indica*, *Boesenbergia rotunda*, *Boswellia serrata*, *Caesalpinia sappan*, *Caligonum polygonoides*, *Camellia sinensis*, *Capsicum baccatum*, *Carica papaya*, *Centella asiatica*, *Cinnamomum verum*, *Corchorus olitorius*, *Corydalis govaniensis*, *Crateva adansonii*, *Crepis sancta*, *Cryptolepis sanguinolenta*, *Curcuma longa*, *Cyrtomium fortune*, *Edgeworthia gardneri*, *Eucalyptus globulus*, *Euphorbia hirta*, *Fagara zanthoxyloides*, *Fragaria ananassa*, *Fructus forsythia*, *Fumaria indica*, *Fumaria vaillantii*, *Geranium thunbergia*, *Glossocalyx brevipes*, *Glycyrrhiza glabra*, *Glycyrrhiza radix*, *Helianthus annuus*, *Hymenocardia acida*, *Hypoxis hemerocallidea*, *Ipomoea batatas*, *Irvingia gabonensis*, *Isatis indigotica*, *Justicia adhatoda*, *Litchi chinensis*, *Lonicerae japonicae*, *Monodora angolensis*, *Moringa oleifera*, *Nerium oleander*, *Nigella sativa*, *Ocimum sanctum*, *Phyllanthus emblica*, *Phyllanthus niruri*, *Piper nigrum*, *Plectranthus amboinicus*, *Pogostemonis herba*, *Psidium guajava*, *Radix astragali*, *Radix platycodonis*, *Radix saphoshnikoviae*, *Rubus coreanus*, *Scutellaria baicalensis*, *Strobilanthes cusia*, *Strychnos nux-vomica*, *Strychnos usambarensis*, *Sutherlandia frutescens*, *Syzygium aromaticum*, *Teclea trichocarpa*, *Terminalia catappa*, *Terminalia chebula*, *Tinospora cordifolia*, *Toddalia asiatica*, *Torreya nucifera*, *Tridax procumbens*, *Triphyophyllum peltatum*, *Verbena officinalis*, *Vitex negundo*, *Vitis vinifera*, *Withania somnifera*, *Xysmalobium undulatum* and *Zingiber officinale*.

It was observed that India had maximum qualified articles (36), which means India generated the maximum scientific evidences in exploring medicinal plants for COVID-19 management, which is not at all surprising taking into consideration the rich traditional knowledge possessed by India in terms of "Ayurveda," "Unani," and "Siddha" medicine. Out of the 78 plants that qualified as per the established criteria, 25 of them were already present in the common antiviral medicinal plant data bank given above (from 2015–2019). Such plants have been marked "*" to indicate their possible role in COVID-19 management.

3.2 | Phytoconstituents and virus interception

Phenolics and flavonoids are common in most of the medicinal plants and they play a positive interceptive role in the pathogenesis of almost all diseases. It can be anticipated that plants rich in such entities are likely to exhibit better biological activity. However, it can also be opined that these entities are alone not solely responsible for the antiviral action but they may provide assistance to the major bioactive compounds. With so many phytoconstituents responding positively for antiviral property, it becomes difficult to comment on the exact therapeutic mode of action. Rather, it can be believed that these phytoconstituents act through a multi-modal approach hitting either multiple therapeutic targets or hitting a specific therapeutic target through multiple pathways for elicitation of the desired action. Viruses can evolve new invasion, propagation, and evasion strategies, which become a big challenge in the development of antivirals (Swamy, 2020). It should also be kept in mind that viruses survive and propagate inside the host cell and it is almost impossible to impact the virus without triggering adverse events on the host cell; inside which the virus is surviving (Denaro et al., 2020). This is where most of the synthetic antivirals have caused havoc. The biggest advantage with such plant bioactive compounds is involvement of one particular entity in various stages of an active virus life cycle as depicted in Figure 3. The mechanism can be understood in light of the different stages occurring in the life cycle of a virus (Figure 3). Plant-based bioactive compounds are likely to cause nil or significantly lesser adverse effects on the host cells while impacting the virus when compared to their synthetic counterparts. Nevertheless, it should be also borne in mind that the possibility of causing adverse effects does not only depend on the toxicity profile of the bioactive compound but the pharmacokinetic and pharmacodynamic interactions also have a lot to play in this regard. Given this condition, plant bioactive compounds cannot be fully assumed to be safe unless their pharmacokinetic/pharmacodynamic interactions are carefully investigated, particularly when plant extracts are administered in tandem with other synthetic antiviral drugs (Denaro et al., 2020).

The different interceptions occurring at different stages of viral replication are: STAGE I: Blocking of virus binding to receptors present on the host cell surface and thus preventing entry of the virus into the host cell through endocytosis. It can be achieved by modulating the viral surface structure and changing the configuration of viral surface proteins, which are actually responsible for binding to host cell receptors, which is a prerequisite step for virus entry (Kapoor, Sharma, & Kanwar, 2017). At STAGE II, Inhibition of viral replication may occur by targeting DNA/RNA polymerase or by modification of viral proteins, inactivation of those enzymes that support growth of the virus like RNA polymerase, protease, and reverse transcriptase (Ahmad & Tyrrell, 1986), inhibition of viral RNA synthesis (Mahomoodally, Gurib-Fakim, & Subratty, 2005), inhibition of neuraminidase (Air & Laver, 1989), binding to viral nucleoprotein thus restraining viral replication (Zhao et al., 2013), creating a cytotoxic environment inside the host cell thus impeding replication of virus (Aiken & Chen, 2005), restraining the proper structural formation, and inhibiting genes for GP2 spike, GP5 membrane protein, and GP6

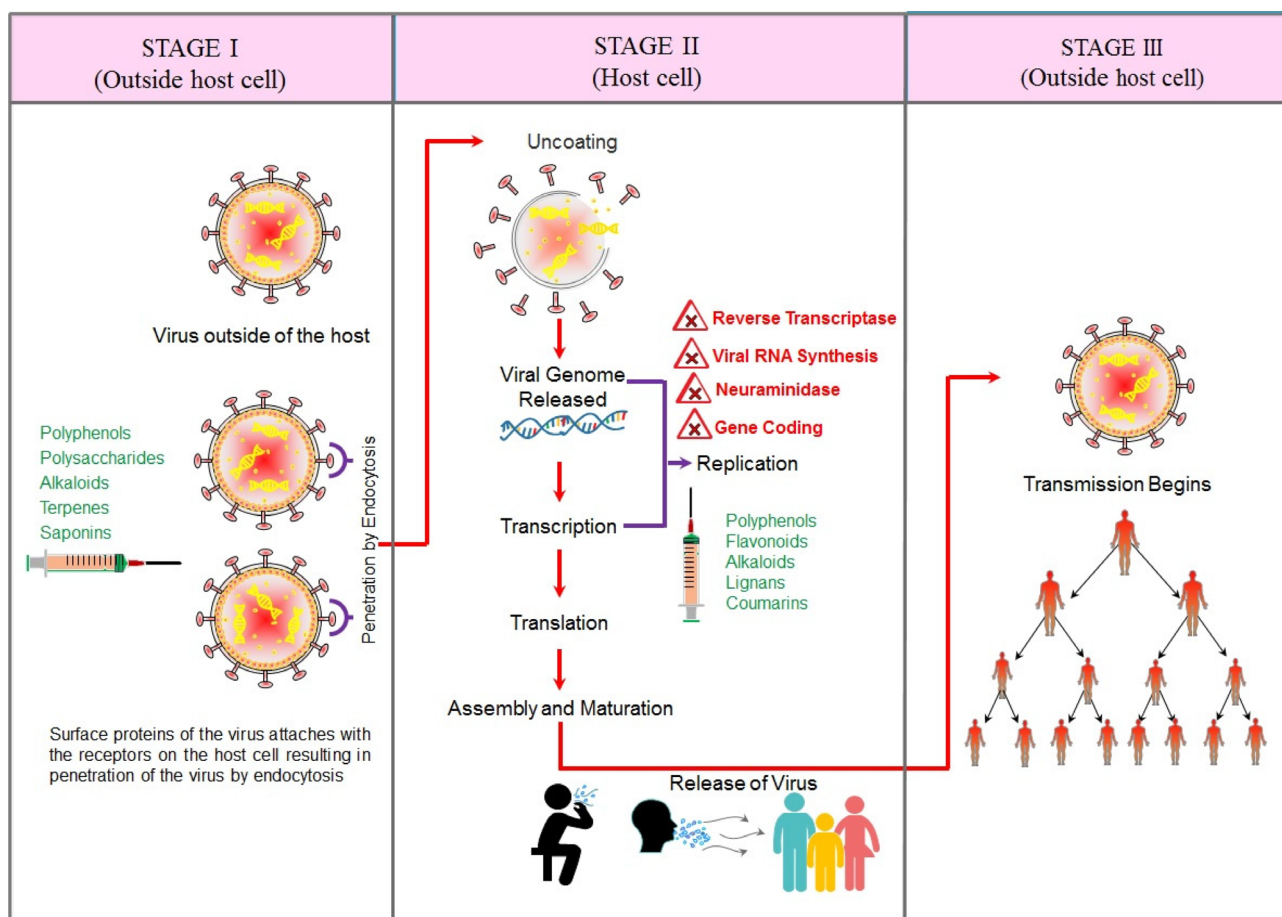


FIGURE 3 Illustrative representation of possible viral interception by plant bioactives. Reverse Transcriptase, Viral RNA synthesis, Neuraminidase, Gene coding indicates probable inhibition routes (🇮🇳) [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.com)]

nucleocapsid (Grigore, Cord, Tanase, & Albulescu, 2020). Nevertheless, an exhaustive compilation of possible modes of antiviral action reported to have been exhibited by plant bioactive compounds is presented in Table 2, which highlight possible impact modes on all viruses including SARS-CoV-2. At STAGE III, evasion of virus takes place, which is then ready to infect others. However, if STAGE-II gets suppressed, it leads to eventual inhibition of STAGE III.

The beauty of these plant bioactive compounds is that they can simultaneously carry out virus interception at both Stages I and II, whereas their synthetic counterparts are capable of virus interception at only one particular stage. Henceforth, plant based bioactive compounds are versatile in nature when it comes to disease mitigation. The abovementioned bioactive compounds even have the potential to participate actively in both innate and adaptive immune responses, probably strengthening it further for combating the viral threat. Such bioactive compounds also can effectively manage the cytokine storm generated during a viral infection, particularly those that are likely to cause respiratory distress (Brendler et al., 2020). The biggest advantage shall be in dealing with mutated viral strains. During a pandemic or epidemic, it is often normal for a virus to get mutated and come out as a more powerful variant. Under such circumstances, synthetic drugs may be rendered useless as they have a fixed mode of action,

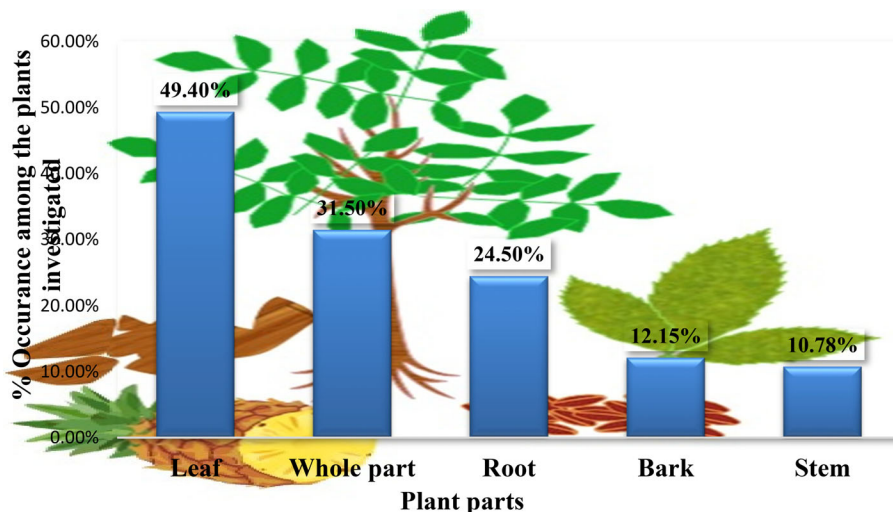
which no longer may be effective for the mutated variant. Phytoconstituents act through various multi-modal therapeutic approaches, henceforth they are in a better position to combat mutated variants when compared to their synthetic counterparts. This database is very likely to assist the researchers in the near future, exercising more judicious decision in plant selection, particularly for investigating antiviral action. Certainly, the COVID situation will sensitize several researchers to explore solutions available in nature for combating viral diseases and that is where this review shall play a pivotal role in the decision-making process regarding plant selection, which is a key step in medicinal plant research.

3.3 | Plant parts used

The various plant parts that were used for antiviral research between 2015 and 2019 were mapped down and are represented in Figure 4. Results indicated that out of 510 plants that were studied in the said tenure, the usage of leaves was estimated to be the most, amounting to 49% followed by usage of whole part (31.5%) and usage of roots amounting to 24.5%. The usage of leaves can be understood in light of the facts that most of the plant bioactive compounds are stored in

TABLE 2 Possible modes of virus interception (including SARS-CoV-2) reported to have been exhibited by plant bioactive compounds

Plant bioactive compounds	Impact point on virus	Impact point on virus (SARS-CoV-2)
Phenolic acid and polyphenols (curcumin, theaflavin, isothaflavin, etc.)	Blocks virus entry or attachment to host cell	Viral infusion inhibition
	Virus absorption inhibition	Viral infectivity inhibition
Flavonoids (hesperidin, apigenin, luteolin, quercetin, etc.)	Replication inhibition and selective inhibition of viral RNA	Blocking of uncoating process
		Inhibition of interaction of SARS-CoV S protein and ACE2
Alkaloids (tetrandrine, emetine, berbamine, etc.)		Increased IL-8 level with significant change in expression of TRPA1, TRPC4, TRPM6, TRPM7, TRPM8, and TRPV4 genes
Glycosides (saikosaponin A/B2/C/D, juglanin, hygromycin B, etc.)	Reduction of viral protein expression	Plaque reduction
Terpenes	Virucidal effect	Viral envelope interference and disruption
Lignans (hinokinin, savinin, etc.)	Immunomodulatory effect	NS3 protease/NS5B polymerase inhibition
Essential oils (linalool, carvacrol, borneol, eugenol, etc.)	NF-kb signaling pathway modulation	Viral particle inactivation
	Cytopathic effect	Inhibition of neuraminidase, protease, reverse transcriptase and integrase—These are essential glycoproteins required for viral replication in host cell
Sterols (sideroxol, β -bisabolene, β -sitosterol, etc.)	Early post-virus binding interference	
	Virus induced pro-inflammatory mediator inhibition	

FIGURE 4 Graphical representation of different plant parts used for antiviral research between 2015 and 2019 [Colour figure can be viewed at wileyonlinelibrary.com]

leaves; large collection of biomaterials is possible as leaves can be easily grown by the plants, hence posing no threat to life of the plant and hence local biodiversity is also not threatened as plants are not killed. But the same is not applicable in collection of whole plant and roots as both of them lead to ultimate death of the plant, which eventually can hamper local biodiversity and large amount of collection of biomaterial also becomes a matter of concern (Mandal & Tandey, 2016).

3.4 | Plant extract and isolates

Various types of extracts were found to have been investigated for antiviral activity (Figure 5). The three most commonly used extract types are ethanolic extract, methanol extract, and aqueous extract. Out of the various types of extracts prepared from the identified 510 plants that were studied, 42.1% were ethanolic extracts, followed

by methanolic extract (31.3%), and aqueous extract contributing 18.6%. However, there are no surprises in these data as the three identified extract types are the most commonly used in natural product research. The use of methanol could be of some minor concern as it is toxic to human body and it should be mandatorily ensured that even trace quantities of methanol have been removed from the final product (extract) before consumption (Singh Chouhan, Tandey, Sen, Mehta, & Mandal, 2020). Nevertheless, all the three solvents offer excellent solubility of phytoconstituents and compatibility as well. Henceforth, it would be a judicious decision to begin the extraction of crude drug with ethanol or even a hydro-alcoholic mixture could also be used.

Some of the major bioactive compounds that have been isolated from the extracts studied for antiviral property are acylphloroglucinol, afzelin, ajwain oil, alternariol, andrographolide, anrotrin A, apigenin, asprellcoside A, astragalol, baicalin, basimarols A, B, C, chebulagic acid, cimicifugic acid, clemastanin B, coumaric acid, cyanversicoside A, cyanversicoside C, embelin, eucalyptin, fukinolic acid, galactomannans, gallic acid, ginsenoside, grandinol, henrin A, hesperidin, hyperin,

kaempferol, khayanolides, loliolide, luteolin, lycorine, myricetin, naringin, neoastilbin, nimbaflavone, nimbin, oblongifolin M, oleanolic acid, plumieride, rosmarinic acid, rutin, scopoletin, sugiol, tangeretin, ursolic, vanillic Acid, vitisin A, vitisin B, wilsonol C, xanthopurpurin, ziyuglycoside I and II, and zoanthone A (Abad, Bermejo, Villar, Sanchez Palomino, & Carrasco, 1997).

However, the above list is just a glimpse of the possible bioactive compounds that could be present in an “antiviral active extract.” Nevertheless, these constituents cannot be held solely responsible for exhibiting the said bioactivity but could participate in a synergistic mode of action. These bioactive compounds can definitely be used as biomarkers for standardization of an “active antiviral extract.”

3.5 | Virus type

Some of the most popular viruses that have been studied in the said tenure are depicted in Figure 6. Search results followed by manual data sorting indicate that from the total number of plants that were

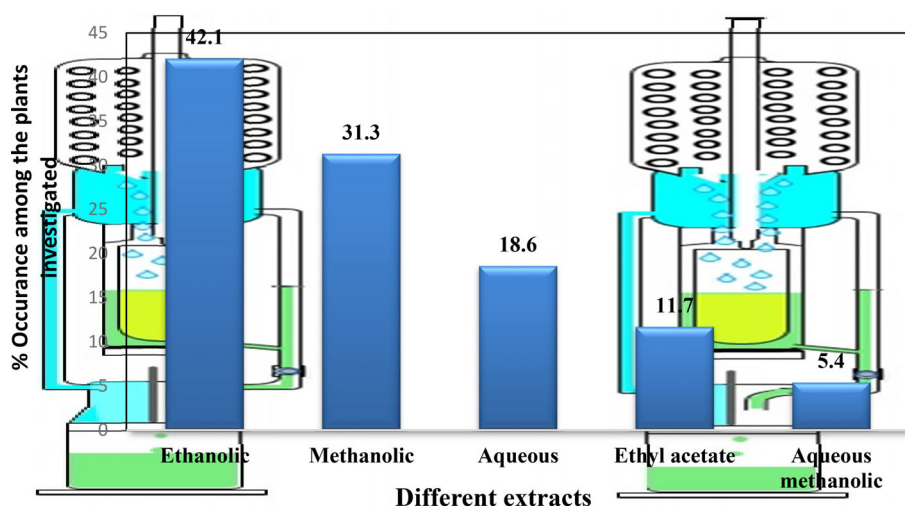


FIGURE 5 Graphical representation of different extract types used for antiviral research between 2015 and 2019 [Colour figure can be viewed at wileyonlinelibrary.com]

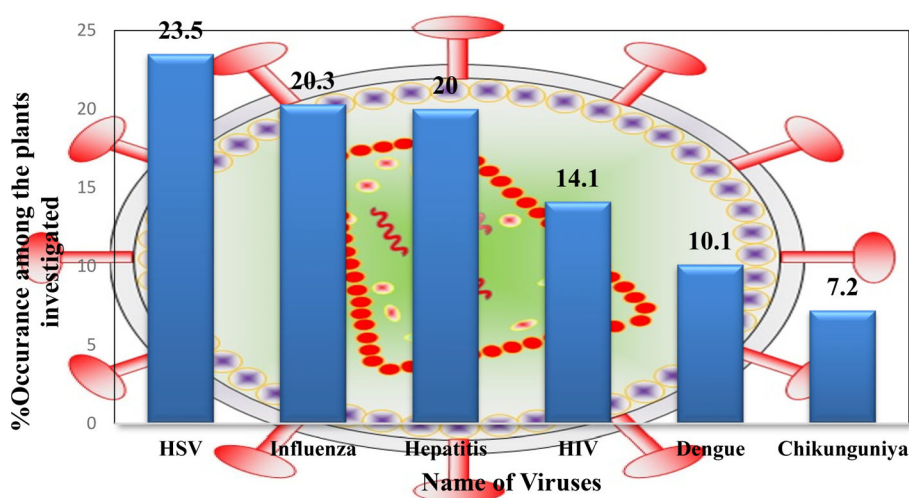


FIGURE 6 Graphical representation indicating the most investigated viruses with respect to the total number of plants identified between 2015 and 2019. HSV (inclusive of HSV-1), Influenza (inclusive of Influenza A, H1N1), Hepatitis (inclusive of Hepatitis C and B), Dengue (inclusive of Dengue type-2) [Colour figure can be viewed at wileyonlinelibrary.com]

screened for antiviral activity in the said tenure, 23.5% of medicinal plants were investigated for herpes simplex virus (HSV), which belongs to a large family of DNA viruses with a broad range of host. According to one of the recently published article, HSV has been said to be the most prevalent and infectious virus (Denaro et al., 2020). Our findings from Scopus data mining successfully indicates a distinct research trends toward investigating medicinal plants for finding a possible solution for HSV, which has been globally recognized as the need of the hour. According to the updates posted on the WHO webpage, it is said that about half a billion people worldwide are living with genital herpes, and several billion have an oral herpes infection. WHO states that an estimated 491.5 million people were living with HSV-2 infection in 2016, equivalent to 13.2% of the world's population aged 15–49 years (James et al., 2020). An estimated 3.7 billion people had HSV-1 infection during the same year, which is around 66.6% of the world's population aged 0–49. Furthermore, WHO has also reported a strong association of herpes virus with the risk of acquiring HIV (James et al., 2020). According to WHO, a strong association exists between HSV-2 infection and HIV infection. According to a modeling study conducted by WHO in 2019, it was estimated that almost 30% of new sexually acquired HIV infections in 2016 worldwide were likely attributable to HSV-2 infection (WHO., 2019). According to WHO as per 2012 data; the estimates of prevalence of HSV-1 by region among people aged 0–49 indicate that South-East

Asia (432–458 million), Africa (350–355 million), Europe (187–207 million), and America (142–178 million) are the worst affected (WHO., 2012). The second most investigated virus is Influenza virus (inclusive of H1N1) belonging to the Orthomyxoviridae family (negative-sense RNA viruses). Filtered data indicated that almost 20.3% of the total plants were investigated for Influenza virus between 2015 and 2019. Influenza virus is well known for pandemics as the story dates back to the dangerous Spanish flu in 1918. According to 2012 data; WHO reported that annual influenza epidemics resulted in about 3–5 million cases of severe illness and about 250,000–500,000 deaths worldwide (WHO, 2012). After the 2009 H1N1 outbreak and the current existing COVID-19 pandemic, it is high time that more research should be directed toward this area and that is what researchers have exactly done as per our filtered data. Researchers have aggressively looked toward nature in finding solutions for combating such infectious if not deadly viruses. A direct correlation can be observed between the different viruses that have been studied most and their infection and outbreak likeliness. This fact indicates that research trends in finding effective antiviral from medicinal plants are greatly inspired by the current understanding on the prevalence intensity of these viruses in a particular country. Figure 7 indicates the countries that have contributed the most in terms of exploring medicinal plants for potential antiviral leads for combating various viral diseases. Research trends of Indian researchers are very clear as they

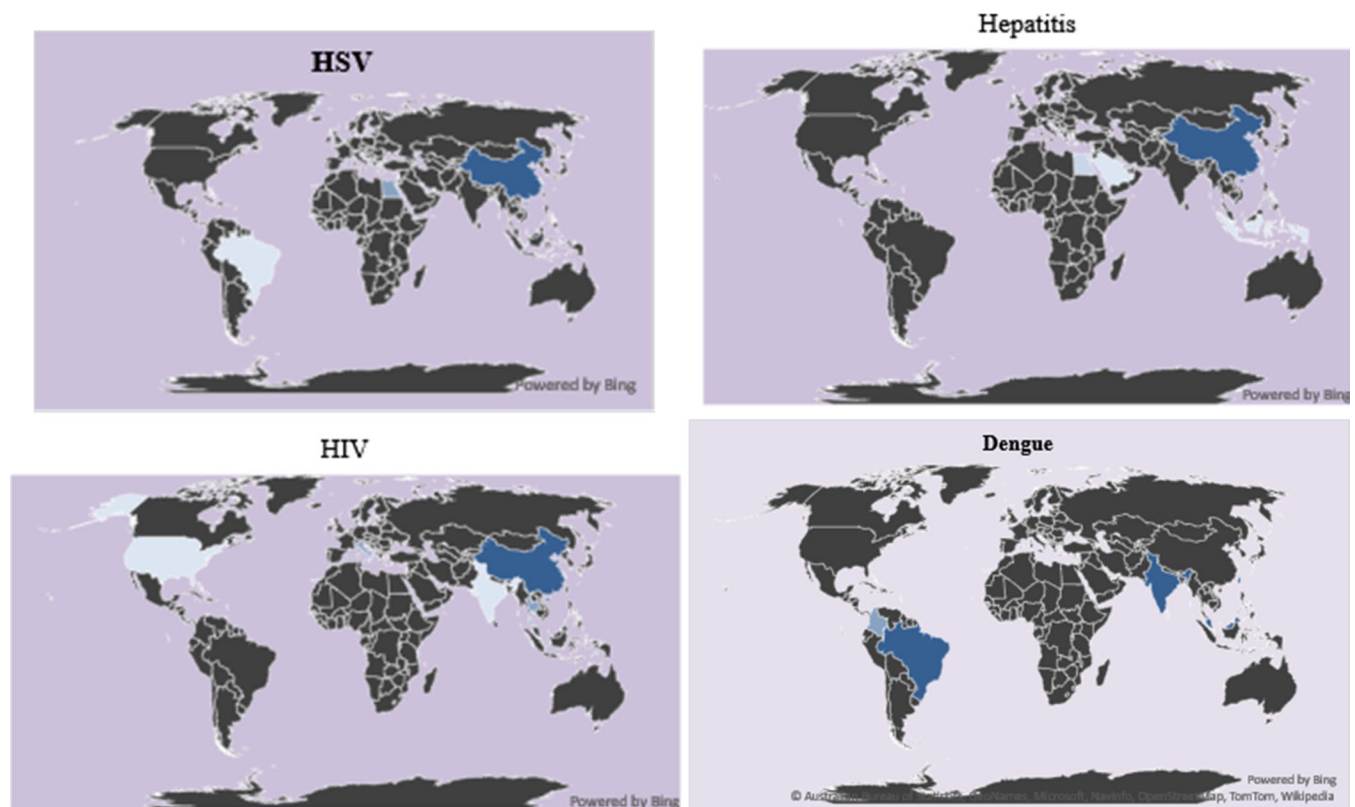


FIGURE 7 World map reflecting those countries that have explored the most number of medicinal plants for a particular virus. HSV (inclusive of HSV-1), Influenza (inclusive of Influenza A, H1N1), Hepatitis (inclusive of Hepatitis C and B), Dengue (inclusive of Dengue type-2). Ranking indicated by color shades [Colour figure can be viewed at wileyonlinelibrary.com]

have targeted those viruses that trouble India the most. In this list; dengue and chikunguniya are the most troubling customers nevertheless, not undermining the lethality of influenza virus particularly in light of the outbreak of H1N1 in India. Both dengue and chikunguniya are vector-borne diseases and their prevalence in India is very high. According to the National Vector Borne Disease Control Programme under the Ministry of Health & Family Welfare (Government of India), the total number of dengue cases reported between 2015 and 2019 is 675,987 (National Health Mission., 2020). Interestingly, China happens to perform more research in exploring medicinal plants for combating viral diseases that can be very well understood in light of the richness associated with Traditional Chinese Medicine (Wu et al., 2020). Countries that have a rich history of traditional medicine must make attempts to find answers to viral threats by digging deep into their own history of traditional medicine. Probably the answer lies within and just needs a deeper exploration. The more we move back into our history, the better we can plan our progress ahead in the future.

In light of the above facts, which have been extracted deep from the history, the likely tutelage presented below may go a long way in reviving the research interest in exploring natural products for combating viral diseases.

1. The roots of the decision of plant selection for investigating antiviral action lie in the ancient traditional medicinal culture of that particular country. It can be believed that a solution for nature's curse (different diseases) lies within nature itself.
2. The 510 names of medicinal plants that have been handpicked through annual sorting of data published between 2015 and 2019 shall serve as a medicinal plant data bank for researchers
3. Polyherbal extracts may be preferred. For the purpose of standardization of such extracts, it is not necessary to isolate a pure compound having antiviral action. A brief directory of several common and specific bioactive compounds has been presented in this article, which can be handpicked for the purpose of standardization. Certain commonly used plant families have been mentioned, which shall also provide a lead in selecting medicinal plants for future investigation
4. Instead of isolating pure compounds, bioactive enriched fractions may be targeted for delivery of better therapeutic value. A holistic approach is likely to yield better results.
5. Having such a large database of plants at our disposal through the widely practiced ancient traditional medicines of various countries, their potential in inhibiting viral proteins should be studied through molecular docking studies and evaluated with design-build-test-learn cycle to assess the true therapeutic values of such plants and bioactive compounds. More research in developing a digital library reflecting capabilities of plant extracts that are concoctions of rich bioactive compounds in inhibiting viral proteins would provide researchers vital leads in optimizing such plant concoctions for circumventing viral threats in future.
6. Plants can be used as bio-factories for the expression as recombinant molecules through the concept of bio-farming, which lays the

foundation stone for plant-based vaccines. Plant vaccines provide far better feasibility in terms of transport, storage, monitoring, and large-scale immunization, which press hardly on the future need of such vaccines, which can be understood well in light of the ongoing large-scale immunization drive being planned against COVID-19. In this regard, plant-based vaccines against Influenza virus, hepatitis B, and rabies are already under clinical trials (Rybicki, 2014).

7. Metabolic engineering in tandem with tissue culturing is one important area in upscaling the yield of plant-based bioactive compounds. Their yield obtained through plant extraction is often less as plants produce very limited quantities of such phytoconstituents and subsequent extraction and purification further results in sample loss. Henceforth, these bioengineering approaches will definitely be critical in ensuring steady supply of such bioactive compounds through engineered process.
8. Combination of known phytochemicals with already approved synthetic antiviral can be explored as it may lead to dose reduction of the synthetic counterpart, causing lesser undesirable side-effects. Genistein, which is a plant-based bioactive, effectively reduced the dose of synthetic drugs acyclovir and ganciclovir when used in combination for the treatment of herpes B virus (Lecher, Diep, Krug, & Hilliard, 2019). At the same time, repurposing of already known phytochemicals with inhibition potential can be tried. Nano-capsulation of such bioactive compounds can be explored for targeted delivery, better bioavailability, and longer duration of action.

4 | CONCLUSIONS

Plant selection in natural product research is always a challenging task. A judicious selection is the key to success, whereas a random selection lacking a wise decision process can result in replicating what already has been done, thus severely jeopardizing the objective of the said research. Researchers tend to refer mainly to research studies in the literature, which are available in scattered form and ethnobotanical evidences, which need deeper exploration, for plant selection. The findings of this review article are expected to serve as a data bank bringing all research literature under one umbrella, thus simplifying the plant selection process for researchers regarding antiviral research. This review article is likely to help the researchers in understanding the research trends pertaining to antiviral research, thus providing vital leads that are likely to serve as starting material for planning research related to antiviral. In simpler words, this review article shall serve as a powerful medicinal plant information directory pertaining to antiviral research. The current review article is not about exemplifying a particular medicinal plant or plant family for antiviral activity based on past literature, neither does this review makes any attempt to understand the pathogenesis and transmission dynamics of a particular virus. Such review articles are traditional reviews and serve only as a collection of known information under one roof. Rather, this review article serves as a status report of all types of

research studies done for finding a possible antiviral solution from medicinal plants between 2015 and 2019. This review intends to present filtered carefully sorted data that will just set the right ambience for the researchers to understand the research trends pertaining to search of antiviral from plants and act accordingly. Critical analysis of the data has been presented, which will serve as a basic guiding force for researchers interested in exploring medicinal plants for finding possible antiviral leads. This review article also showcases the strength of nature in terms of exploring medicinal plants for combating various viral threats, which may have a pandemic potential. Vaccines could be the ultimate answers for all types of viral illness but researchers need to find alternative pathways for combating such threats until vaccines are in sight. Synthetic antiviral drugs can play havoc in terms of compromising the human biological system by creating various undesirable side-effects, which have become evident during this COVID pandemic. This review is expected to serve as a rich database and as a guiding principle for researchers who are planning to explore medicinal plants in search for potential antiviral. It is time that researchers need to revisit their countries' own history of traditional medicine to predict something worthwhile in future. If nature has given a problem, we must believe that the solution also lies within, which may just need a deeper exploration into the history. The ongoing viral pandemic has taught us those toughest lessons of life, which otherwise we could never have learned. This review article is just a pro-active step so that next time when we are hit, we should not be caught unprepared.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest associated with this article.

DATA AVAILABILITY STATEMENT

Data derived from public domain resources

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REFERENCES

- Abad, M. J., Bermejo, P., Villar, A., Sanchez Palomino, S., & Carrasco, L. (1997). Antiviral activity of medicinal plant extracts. *Phytotherapy Research*, 11(3), 198–202. [https://doi.org/10.1002/\(SICI\)1099-1573\(199705\)11:3<198::AID-PTR78>3.0.CO;2-L](https://doi.org/10.1002/(SICI)1099-1573(199705)11:3<198::AID-PTR78>3.0.CO;2-L)
- Ahmad, A. L. M., & Tyrrell, D. A. J. (1986). Synergism between anti-rhinovirus antivirals: Various human interferons and a number of synthetic compounds. *Antiviral Research*, 6(4), 241–252. [https://doi.org/10.1016/0166-3542\(86\)90005-7](https://doi.org/10.1016/0166-3542(86)90005-7)
- Aiken, C., & Chen, C. H. (2005). Betulinic acid derivatives as HIV-1 antivirals. *Trends in Molecular Medicine*, 11(1), 31–36. <https://doi.org/10.1016/j.molmed.2004.11.001>
- Air, G. M., & Laver, W. G. (1989). The neuraminidase of influenza virus. *Proteins: Structure, Function, and Bioinformatics*, 6(4), 341–356. <https://doi.org/10.1002/prot.340060402>
- Antonio, A. D. S., Wiedemann, L. S. M., & Veiga-Junior, V. F. (2020). Natural products' role against COVID-19. *RSC Advances*, 10(39), 23379–23393. <https://doi.org/10.1039/d0ra03774e>
- Arceusz, A., Radecka, I., & Wesolowski, M. (2010). Identification of diversity in elements content in medicinal plants belonging to different plant families. *Food Chemistry*, 120(1), 52–58. <https://doi.org/10.1016/j.foodchem.2009.09.068>
- Brendler, T., Al-Harrasi, A., Bauer, R., Gafner, S., Hardy, M. L., Heinrich, M., ... Williamson, E. M. (2020). Botanical drugs and supplements affecting the immune response in the time of COVID-19: Implications for research and clinical practice. *Phytotherapy Research*, 1–19. <https://doi.org/10.1002/ptr.7008>
- Carović-Stanko, K., Petek, M., Grdiša, M., Pintar, J., Bedeković, D., Herak Čustić, M., & Satovic, Z. (2016). Medicinal plants of the family Lamiaceae as functional foods – A review. *Czech Journal of Food Sciences*, 34(5), 377–390. <https://doi.org/10.17221/504/2015-CJFS>
- Chouhan, K. B. S., Tandey, R., Sen, K. K., Mehta, R., & Mandal, V. (2019). Critical analysis of microwave hydrodiffusion and gravity as a green tool for extraction of essential oils: Time to replace traditional distillation. *Trends in Food Science and Technology*, 92, 12–21. <https://doi.org/10.1016/j.tifs.2019.08.006>
- Ciotti, M., Ciccozzi, M., Terrinoni, A., Jiang, W. C., Wang, C. B., & Bernardini, S. (2020). The COVID-19 pandemic. *Critical Reviews in Clinical Laboratory Sciences*, 57(6), 1–24. <https://doi.org/10.1080/10408363.2020.1783198>
- Denaro, M., Smeriglio, A., Barreca, D., De Francesco, C., Occhiuto, C., Milano, G., & Trombetta, D. (2020). Antiviral activity of plants and their isolated bioactive compounds: An update. *Phytotherapy Research*, 34(4), 742–768. <https://doi.org/10.1002/ptr.6575>
- Fazal, U., & Islam, S. (2019). The pharmacological and medicinal importance of the species of lamiaceae family, a review study. *Journal of Clinical Trials and Regulations*, 1(2), 17–23.
- Grigore, A., Cord, D., Tanase, C., & Albulescu, R. (2020). Herbal medicine, a reliable support in COVID therapy. *Journal of Immunoassay and Immunochromatography*, 41(6), 1–24. <https://doi.org/10.1080/15321819.2020.1862867>
- Halberstein, R. A. (2005). Medicinal plants: Historical and cross-cultural usage patterns. *Annals of Epidemiology*, 15(9), 686–699. <https://doi.org/10.1016/j.annepidem.2005.02.004>
- Hussain, S., Xie, Y. J., Li, D., Malik, S. I., Hou, J. C., Leung, E. L. H., & Fan, X. X. (2020). Current strategies against COVID-19. *Chinese Medicine (United Kingdom)*, 15(1), 1–12. <https://doi.org/10.1186/s13020-020-00353-7>
- Islam, M. T., Sarkar, C., El-Kersh, D. M., Jamaddar, S., Uddin, S. J., Shilpi, J. A., & Mubarak, M. S. (2020). Natural products and their derivatives against coronavirus: A review of the non-clinical and pre-clinical data. *Phytotherapy Research*, 34(10), 2471–2492. <https://doi.org/10.1002/ptr.6700>
- James, C., Harfouche, M., Welton, N. J., Turner, K. M. E., Abu-Raddad, L. J., Gottlieb, S. L., & Looker, K. J. (2020). Herpes simplex virus: Global infection prevalence and incidence estimates, 2016. *Bulletin of the World Health Organization*, 98(5), 315–329. <https://doi.org/10.2471/BLT.19.237149>
- Kalil, A. C. (2020). Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA - Journal of the American Medical Association*, 323(19), 1897–1898. <https://doi.org/10.1001/jama.2020.4742>
- Kang, Y. M., Komakech, R., Karigar, C. S., & Saqib, A. (2017). Traditional Indian medicine (TIM) and traditional Korean medicine (TKM): A constitutional-based concept and comparison. *Integrative Medicine Research*, 6(2), 105–113. <https://doi.org/10.1016/j.imr.2016.12.003>

- Kapoor, R., Sharma, B., & Kanwar, S. S. (2017). Antiviral phytochemicals: An overview. *Biochemistry & Physiology: Open Access*, 06(02), 220–227. <https://doi.org/10.4172/2168-9652.1000220>
- Koc, S., Isgor, B. S., Isgor, Y. G., Shomali Moghaddam, N., & Yildirim, O. (2015). The potential medicinal value of plants from Asteraceae family with antioxidant defense enzymes as biological targets. *Pharmaceutical Biology*, 53(5), 746–751. <https://doi.org/10.3109/13880209.2014.942788>
- Lecher, J. C., Diep, N., Krug, P. W., & Hilliard, J. K. (2019). Genistein has antiviral activity against herpes B virus and acts synergistically with antiviral treatments to reduce effective dose. *Viruses*, 11(6), 499. <https://doi.org/10.3390/v11060499>
- Mahomoodally, M. F., Gurib-Fakim, A., & Subratty, A. H. (2005). Antimicrobial activities and phytochemical profiles of endemic medicinal plants of Mauritius. *Pharmaceutical Biology*, 43(3), 237–242. <https://doi.org/10.1080/13880200590928825>
- Mandal, V., Chouhan, K. B. S., Tandey, R., Sen, K. K., Kala, H. K., & Mehta, R. (2018). Critical analysis and mapping of research trends and impact assessment of polyaromatic hydrocarbon accumulation in leaves: Let history tell the future. *Environmental Science and Pollution Research*, 25(23), 22464–22474. <https://doi.org/10.1007/s11356-018-2578-x>
- Mandal, V., & Tandey, R. (2016). A critical analysis of publication trends from 2005–2015 in microwave assisted extraction of botanicals: How far we have come and the road ahead. *TrAC Trends in Analytical Chemistry*, 82, 100–108. <https://doi.org/10.1016/j.trac.2016.05.020>
- Meijer, D. K. F., Jansen, R. W., & Molema, G. (1992). Drug targeting systems for antiviral agents: Options and limitations. *Antiviral Research*, 18, 215–258.
- More, A. F., Loveluck, C. P., Clifford, H., Handley, M. J., Korotkikh, E. V., Kurbatov, A. V., ... Mayewski, P. A. (2020). The impact of a six-year climate anomaly on the “Spanish flu” pandemic and WWI. *GeoHealth*, 4(9), e2020GH000277. <https://doi.org/10.1029/2020GH000277>
- National Health Mission. (2020). Dengue situation in India. Retrieved from <https://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=431&lid=3715>
- Nayeem, N., & Mehta, S. K. (2015). A review on family lamiaceae with emphasis on some medicinally important plants of the genus Clerodendrum. *International Journal of Universal Pharmacy and Bio-Sciences I*, 4(1), 286–301.
- Rybicki, E. P. (2014). Plant-based vaccines against viruses. *Virology Journal*, 11(1), 1–20. <https://doi.org/10.1186/s12985-014-0205-0>
- Scopus (2020). Retrieved from https://www.scopus.com/results/results.uri?numberOfFields=1&src=s&clickedLink=&edit=&editSaveSearch=&origin=searchbasic&authorTab=&affiliationTab=&advancedTab=&scint=1&menu=search&tablin=&searchterm1=Antiviral&field1=TITLE_ABS_KEY&connector=AND&searchterm
- Singh Chouhan, K. B., Tandey, R., Sen, K. K., Mehta, R., & Mandal, V. (2020). Microwave hydrodiffusion and gravity model with a blend of high and low power microwave firing for improved yield of phenolics and flavonoids from oyster mushroom. *Sustainable Chemistry and Pharmacy*, 17(July), 100311. <https://doi.org/10.1016/j.scp.2020.100311>
- Swamy, M. K. (2020). Phytochemicals as Antiviral Agents: Recent Updates. In *Plant-derived bioactives: Production, properties and therapeutic applications*. (pp. 279–295). USA: Springer Link. https://doi.org/10.1007/978-981-15-1761-7_12
- Thota, S. M., Balan, V., & Sivaramakrishnan, V. (2020). Natural products as home-based prophylactic and symptom management agents in the setting of COVID-19. *Phytotherapy Research*, 34(12), 3148–3167. <https://doi.org/10.1002/ptr.6794>
- Urita, C. M., Mihai, C. T., Stanciu, G. D., Dodi, G., Alexa-Stratulat, T., Luca, A., ... Tamba, B. I. (2018). Medicinal plants of the family Lamiaceae in pain therapy: A review. *Pain Research and Management*, 2018, 1–44. <https://doi.org/10.1155/2018/7801543>
- WHO. (2012). *Progress on drinking water and ...*. Retrieved from <https://www.who.int/news/item/28-10-2015-globally-an-estimated-two-thirds-of-the-population-under-50-are-infected-with-herpes-simplex-virus-type-1>
- WHO. (2019). *Universal health coverage: Strengthening health workforce*. Retrieved from https://www.who.int/health-topics/hiv-aids/#tab=tab_1
- Wu, R., Wang, L., Kuo, H. C. D., Shannar, A., Peter, R., Chou, P. J., ... Kong, A. N. (2020). An update on current therapeutic drugs treating COVID-19. *Current Pharmacology Reports*, 6(3), 56–70. <https://doi.org/10.1007/s40495-020-00216-7>
- Yashaswini, P., Geetha, A., & Prashanth, B. V. (2019). Analysis of pricing of oral antiviral drug formulations available in Indian market. *National Journal of Physiology, Pharmacy and Pharmacology*, 9(5), 401. <https://doi.org/10.5455/njppp.2019.9.0205507032019>
- Zhao, K., Gu, M., Zhong, L., Duan, Z., Zhang, Y., Zhu, Y., ... Liu, X. (2013). Characterization of three H5N5 and one H5N8 highly pathogenic avian influenza viruses in China. *Veterinary Microbiology*, 163(3–4), 351–357. <https://doi.org/10.1016/j.vetmic.2012.12.025>

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