compounds

MDPI

Review

Ethnomedicinal, Phytochemistry and Antiviral Potential of Turmeric (*Curcuma longa*)

Bajarang Bal Lal Srivastava, Asha Shabani Ripanda * and Hossein Miraji Mwanga

Department of Chemistry, College of Natural and Mathematical Sciences, The University of Dodoma, Dodoma P.O. Box 338, Tanzania

* Correspondence: asha.ripanda@udom.ac.tz; Tel.: +255-754846316

Abstract: Turmeric (*Curcuma longa*) has been a famous root crop for its medicinal properties since pre-historical times. Lack of effective therapeutics for most viral diseases, higher cost of some antiviral therapies, and the emergence of antiviral drug resistance are increasingly reported. Drug resistance is predicted to be a leading cause of mortality globally by 2050, thus requiring intervention. The need for effective natural antiviral compounds to mitigate viral diseases, such as curcumin, calls for further studies. Curcumin, a primary curcuminoid compound, has demonstrated a broad activity as an antiviral agent. Due to the need to overcome drug resistance to chemically synthesised drugs, the best option is to improve and adapt the use of natural antiviral agents. The antiviral potential of curcumin is hindered by its solubility and bioavailability. Recently, different techniques, such as the preparation of curcumin carbon quantum dots, have been used to improve curcumin antiviral activity. Therefore, the current review aims to assess curcumin's benefits as a natural antiviral agent and techniques to improve its medicinal activity. Future use of curcumin will aid in mitigating viral diseases, including resistant strain, hence sustainability of the entire community. In this case, research and innovation are required to improve the solubility and bioavailability of curcumin for medical uses.

Keywords: *Curcuma longa*; health benefits; antiviral; pharmacology; chemistry; curcumin nano-formulations

check for updates

Citation: Srivastava, B.B.L.; Ripanda, A.S.; Mwanga, H.M. Ethnomedicinal, Phytochemistry and Antiviral Potential of Turmeric (*Curcuma longa*). *Compounds* **2022**, *2*, 200–221. https://doi.org/10.3390/compounds2030017

Academic Editor: Maria Lurdes Santos Cristiano

Received: 19 June 2022
Accepted: 15 August 2022
Published: 26 August 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Turmeric (*Curcuma longa)* is a blossoming plant of the Zingiberaceae family. Since the prehistoric period, turmeric has been used in Asian medicine as a major part of Ayurveda, Siddha, Traditional Chinese, Unani medicine, and the animistic rituals of Austronesian peoples. It was initially used as a dye and then later for its supposed properties in folk medicine [1]. The plant is a rhizomatous perennial herbaceous native to Southeast Asia and the Indian subcontinent, flourishing in temperate conditions and requiring a significant annual rainfall [2–4]. Mostly the rhizomes are used fresh or boiled in water and dried, after which they are crushed into a deep orange-yellow powder that is commonly used as a colouring and flavouring agent in many Asian cuisines, especially curries, as well as for dyeing, thanks to the properties imparted by curcumin, the main turmeric constituent [2,5–7]. Turmeric powder has an earthy, mustard-like fragrance and a warm, bitter black pepper flavour. Curcuma species diversity is greatest in India, followed by Thailand, and other tropical Asian countries have various wild Curcuma species [5,8–10]. Recent research revealed issues with *Curcuma longa* classification, with only specimens from South India being identified as *C. longa.* Other species and cultivars in other world regions still need their phylogeny, relationships, intraspecific and interspecific variation and even identity to be identified and validated [11]. Multiple species advertised as turmeric in different parts of the world have been found to belong to several visually identical taxa with overlapping local names. Traditional medicinal practices are the main source of primary healthcare providers, especially in developing countries. The World Health Organization (WHO)

reported that about 80% of the global population depends on traditional medicine for their healthcare [12]. Natural product remedies are becoming more popular among developed countries as they see medicinal herbs as safe alternatives to orthodox medicines [13].

1.1. Global Distribution of Curcuma longa

Curcuma longa is native to India and was introduced to other areas such as the Andaman Islands, Assam, Bangladesh, Belize, Borneo, Cambodia, Caroline Islands, China South-Central, China Southeast, Comoros, Congo, Cook Islands, Costa Rica, Cuba, Dominican Republic, East Himalaya, Easter Islands, Fiji, Gilbert Islands, Guinea-Bissau, Gulf of Guinea Islands, Haiti, Hawaii, Ivory Coast, Jawa, Leeward Islands and Lesser Sunda Islands, M [14]. Figure 1 represents the global distribution of *Curcuma longa*.

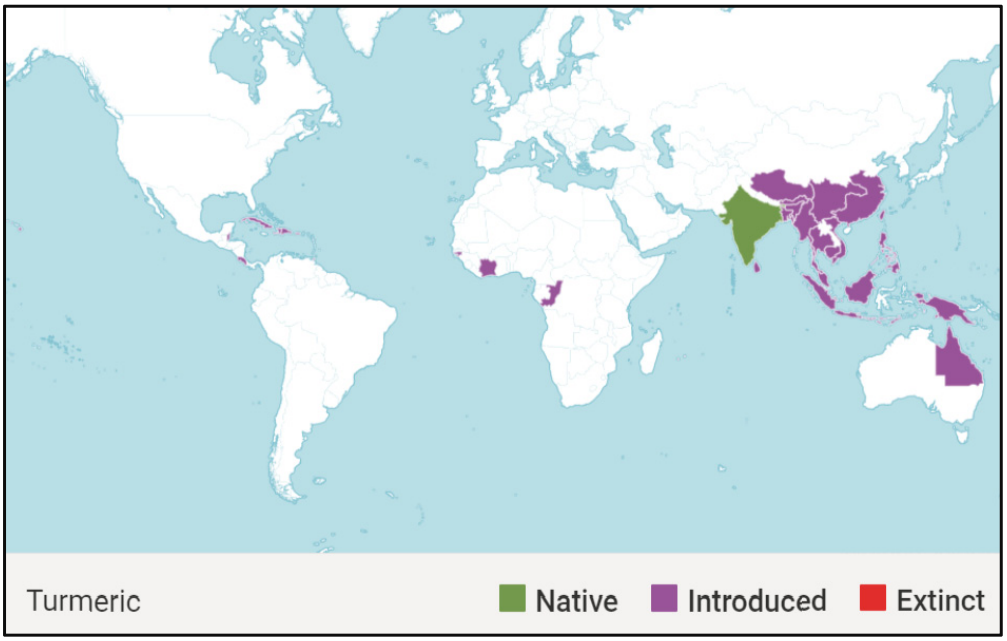


Figure 1. Global distribution of *Curcuma longa* plants [14].

1.2. Morphology of Curcuma longa

Turmeric is a herbaceous perennial plant that grows up to 1 m tall. The rhizomes are branching, bright to orange, cylindrical and scented. The leaves are placed in two rows and alternate. Leaf-sheath, petiole and leaf blade are the three parts of the leaf. A fake stem is created from the leaf sheaths. The petiole can range in length from 50 to 115 cm. Simple leaf blades range in length from 76 to 115 cm, with some reaching up to 230 cm [8,9,11,15,16]. They are 38 to 45 cm wide and oblong to elliptical, narrowing at the tip. Stem bracts, which are white to green in colour and sometimes tinged reddish-purple, are located at the top of the inflorescence and have tapered upper ends. The flowers of hermaphrodites are threefold and zygomorphic. The three sepals are white, united and contain fluffy hairs; the three calyx teeth are uneven. The three vivid yellow petals are united into a 3-centimetre-long corolla tube. The three corolla lobes are triangular with soft-spiny top tips and measure 1.0 to 1.5 cm in length [8,9,11,15,16]. Only the median stamen of the inner circle is fertile, even though the average corolla lobe is larger than the two lateral ones. Figure 2 represents the morphology of curcumin.

The base of the dust bag is spurred. The remaining stamens are transformed into staminodes. The staminodes on the outside are shorter than those on the inside. The labellum is yellowish, with a yellow ribbon in the centre, and is obovate, measuring 1.2 to 2.0 cm in length [11,16]. Three carpels are held in place by a trilobed, sparsely hairy ovary [8,9,11,15,16]. Three sections open up when the fruit capsule is opened. The blossoming season in East Asia is normally in August. An inflorescence stalk, 12 to 20 cm

long and with many flowers, grows at the end of the false stem [11,16]. The bracts are light green and elliptical to oblong shape with a blunt upper end, measuring 3 to 5 cm in length [11,16].

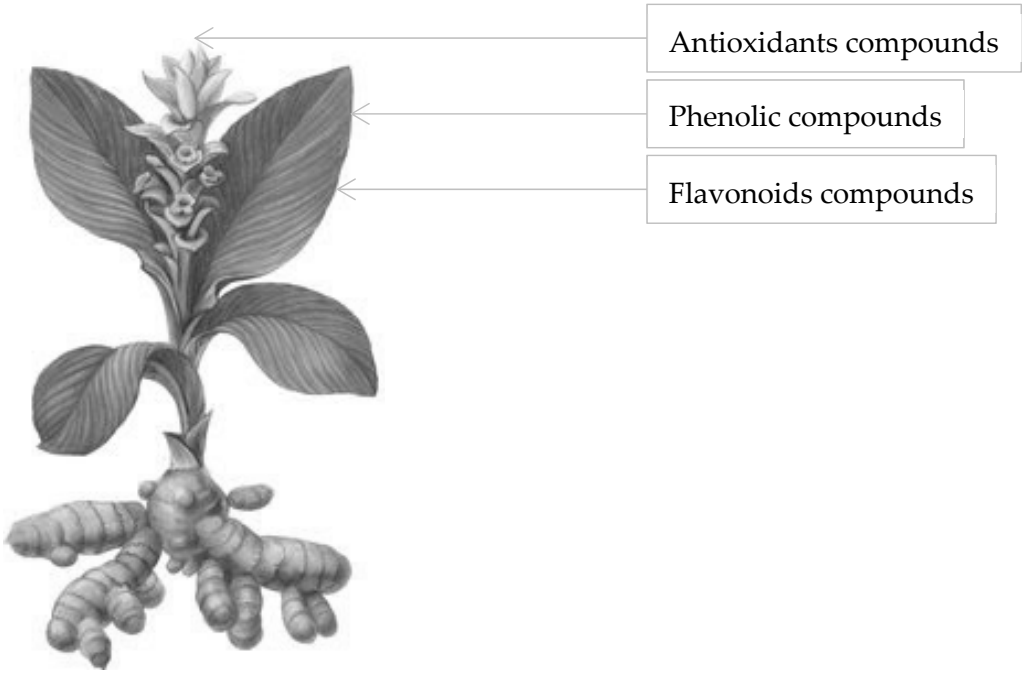


Figure 2. Morphological description of turmeric [17,18].

1.3. Botanical Classification of C. longa

The taxonomic classification of turmeric botanically known as *Curcuma longa* is presented in Table 1.

Table 1. Describes the scientific classification of *C. longa*.

Taxa	Name
Domain	Eukaryota
Kingdom	Plantae
Phylum	Spermatophyta
Subphylum	Angiospermae
Class	Monocotyledonae
Order	Zingiberales
Family	Zingiberaceae
Genus	Curcuma
Species	*Curcuma longa*

1.4. Chemistry of Curcumin

Curcumin has a seven-carbon linker and three major functional groups: an aromatic O-methoxy-phenolic group, an aromatic O-methoxy-phenolic group and an aromatic O-methoxy-phenolic group [19]. Two-unsaturated carbonyl groups join the aromatic ring systems, which are phenols. It is a diketone tautomer in both enolic and keto forms in organic solvents and water [20]. The diketones deprotonate to create enolates and form stable enols; the-unsaturated carbonyl group is a good Michael acceptor and undergoes nucleophilic addition [21]. Curcumin is poorly soluble in water due to its hydrophobic nature [20]. Organic solvents, on the other hand, make it very soluble. Selected structures of the bioactive present in Curcumin are presented in Figure 3.

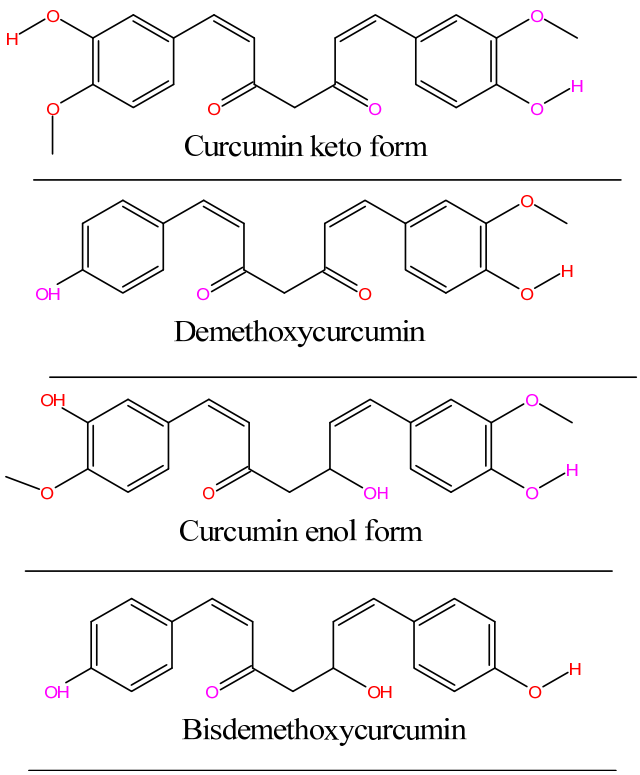


Figure 3. Represents selected structures of the phytochemical constituents present in *Curcuma longa*.

2. Materials and Methods

The scope of this literature review was the potential of curcumin as an antiviral agent and the measures taken to remove barriers to its utility for medical application. *Curcuma longa* is native to India. Figure 1 details its global status through its introduction in other areas, and it is used for medical applications and as a food additive globally. Besides the fact that *Curcuma longa* has been reported to possess other bioactivities, this study focuses only on antiviral potential. This study includes potential studies from 2000 to 2021; apart from the use of *Curcuma longa* from the pre-historic period, a growing trend in published articles was observed from 2000. This may be due to the growing need to source drug candidates from natural products for mitigation of diseases, including resistant strains. The search keywords included *Curcuma longa*, the antiviral potential of *Curcuma longa*; medicinal potential; ethnobotanical uses of *Curcuma longa*; how to improve the bioactivity of *Curcuma longa*; uses of *Curcuma longa*. Web of Science, Scopus, Wiley Online Library, Science Direct, Taylor and Francis Online, Sage Publishing, Scopus, Research for Life, and PubMed were the search engines used for searching scientific journals, and some were hand-picked from Google Scholar. The literature review was performed on papers obtained for the data related to *Curcuma longa, pharmacology, ethnomedicinal use, application, safety, toxicity and medical applicability.* This resulted in a database of data extracted from representative studies for this review. Table 2 represents studies that detail modifications done on *Curcuma longa*-based drug to improve its bioactivity. Table 3 details the antiviral potential of *Curcuma longa*-based drugs, and Table 3 details the antiviral potential of *Curcuma longa.*

3. Pharmacology of Curcumin

Curcumin is a false lead that medicinal chemists classify as "pan-assay interference substances" since it shows up positive in most drug discovery assays. This attracts excessive experimental interest while failing to progress as viable therapeutic or pharmacological leads [22–24]. However, other curcumin derivatives, such as EF-24, have received much attention [25]. Chemical instability, water insolubility, lack of powerful and selective target activity, low bioavailability, limited tissue distribution and extensive metabolism are all

factors that limit curcumin or its analogues' bioactivity [22]. Curcumin escapes the GI system in small amounts, and most of it is eliminated intact in the stool [26]. Because curcumin is promiscuous and interacts with multiple proteins known to enhance the likelihood of adverse effects, such as hERG, cytochrome P450s, and glutathione S-transferase, there is a substantial risk of toxicity if it reaches plasma in moderate concentrations [22]. Diferuloylmethane, commonly curcumin, a natural polyphenolic compound derivative of turmeric (*Curcuma longa*), is a widely used spice and colouring agent in food [27]. Curcumin is commonly included in many therapeutic remedies, singly or with other natural substances [28]. Gathered evidence indicates that curcumin is associated with a great variety of pharmacological activities, such as anti-microbial [1,28–31], anti-inflammatory [32] and antioxidant [33]. Curcumin inhibits several tumours in vitro and in vivo [34,35]. Such effects have been attributed to the interaction of curcumin with a diverse range of molecular targets involved in cell growth, metastasis, tumour angiogenesis and apoptosis; for instance, nuclear factor jB (NF-jB), cyclooxygenase-2, matrix metalloproteinase, vascular cell adhesion molecule-1 and p53 [36]. By inhibiting IjB phosphorylation by IjB kinase, curcumin effectively suppressed NF-jB signalling, which regulates the expression of genes contributing to tumorigenesis and cell survival [37–39].

4. Mechanism of Curcumin Antiviral Activity

According to data, curcumin appears to have an inhibitory effect on the infection of various viruses. These strategies entail direct interference with viral replication machinery or regulation of viral replication-related cellular signalling pathways such as PI3K/Akt and NF-B to exert antiviral activity. Most antiviral drugs, such as curcumin, target important phases in the viral life cycle; a virus cannot contain all the enzymes required for replication as a single unit. Viruses take over cellular machinery to facilitate their replication and metabolic functions. On the other hand, an antiviral agent must limit viral development in infected cells while leaving healthy cells alone. As a result, various steps in the virus's replication cycle, including attachment/penetration, uncoating, genome replication, gene expression, assembly, and release, have been appealing targets for chemotherapeutic intervention. Curcumin's bio-functions include reversing viral infection by targeting viral entry or attacking only the components required for viral reproduction.

4.1. Inactivate Extracellular Virus Particles

Extracellular particles (EPs) have been recently identified as small protein-nucleic acid complexes released by cells, carrying molecular biomarkers and intercellular signals. These particles have been identified using technologies such as asymmetric-flow field-flow fractionation and the nanoscale flow cytometry approach. Although their diameters are 35 nm [40], their origins, biological and structural composition, functionality and release mechanisms are unknown, yet they can modulate the physiological processes of cells. EPs, including exomeres and chromatimeres, have a similar structure and function to extracellular vesicles (EVs) but lack membrane bounding. Being involved in cellular communication, they are responsible for the adaptive immune system and communicate physiological processes such as foetal-maternal crosstalk, embryogenesis, and thrombosis and disease developments. The EPs and EVs are the efficient mechanisms viruses can use to enter host cells, invade the host immune response or enhance spreading [41–43]. Virus particles cannot replicate independently; rather, they enter the cells' active sites. Virus-like particles support the infection, while infectious viral particles induce viral propagation and cellular reprogramming [41,42]. Since EPs and EVs contain infectious viral materials, antiviral drugs must inactivate them before intruding into a cell. Curcuma oil has enhanced immune functioning and antiviral ability and accelerates toxin elimination [44,45]. Liu and Ying reported that the extracellular mechanisms of curcumin could eliminate foreign pathogenic organisms [46]. However, suppression of EV secretion [47] due to antiviral curcumin is not well known.

4.2. Prevent Viral Attachment and/or Entry

The initial event that gets viruses to the cell membrane surface is attachment. Curcumin inhibits the infectivity of several enveloped viruses, including members of the poxvirus, flavivirus, herpesvirus, and orthomyxovirus families, when applied to cells before or during infection, whereas the plaque-forming ability of the non-enveloped enterovirus 71 (EV71) was unaffected [48]. Curcumin also inhibits the action of viral envelope proteins, such as the haemagglutinin-neuraminidase (HN) protein of Newcastle disease virus and the haemagglutinin (HA) protein of IAV, when incubated directly with viruses [48]. According to a recent study, curcumin inhibits the infections of two arthropod-borne viruses, Zika and Chikungunya, by preventing virus binding on the cell surface [49]. In several investigations, curcumin has been found as a membrane modifying agent; in short, the connection with the lipid bilayer induces a non-linear membrane thinning and reduces the membrane's elasticity [50,51]. Curcumin boosted lipid raft formation in MDBK cells, altering the entrance process of bovine herpesvirus type 1 and lowering overall viral output dose-dependent [52]. Curcumin consistently inhibited the entrance of all major genotypes of the hepatitis C virus (HCV) [53,54]. In membrane fluidity assays, the viral entrance was hampered by viral binding and membrane fusion, likely caused by curcumin altering the fluidity of the viral envelope [53–55].

Nonetheless, a non-enveloped virus, human norovirus, showed the action of curcumin at a very early stage of viral infection (HuNoV) [56]. Curcumin therapy at various doses and durations was found to have antiviral mechanisms such as viral entry rather than HuNoV RNA replication [56]. Curcumin may influence viral entry by blocking the activity of viral surface proteins since viral entry involves initial contact between the viral surface protein and the receptor on the host membrane, in the case of HuNov, without the goal of lipid bilayer envelop construction. For example, the damage to IAV HA activity mediated by curcumin is likely due to the interruption of the link between the viral HA molecule and its cellular sialic acid receptor [57]. Curcumin may preoccupy the receptor-binding site on protein with the cellular receptor, as evidenced by in silico docking simulation results [57]. Curcumin pretreatment inhibited viral haemorrhagic septicaemia virus (VHSV) invasion [58]. The decrease may mediate the anti-VHSV effect of curcumin at the early stages of infection in heat shock cognate (HSC71), a protein that plays a central role in various cellular processes during VHSV infection modulate the function of actin, according to comparative proteomic analysis. However, further research is required to determine if direct intermolecular interactions mediate curcumin's activities. Curcumin has been considered a virucidal agent due to its action on the viral envelope or surface proteins. Curcumin pretreatment effectively inhibits plaque development of many enveloped viruses, including IAV, vaccinia virus, pseudorabies virus [48], and RSV, in the liposome model [56]. According to Yang et al., curcumin-modified silver nanoparticles (cAgNPs) have effective antiviral action against RSV infection. Compared to individuals lacking cAgNPs, cAgNPs may reduce the virus's capacity to connect to the binding centres on the cell surface, effectively preventing RSV infection by inactivating RSV before it enters the cell [56].

4.3. Prevent Replication of the Viral Genome

Virus reproduction necessitates interactions between viral components and diverse cellular stimuli as an intracellular parasite. Viral genome replication is typically initiated by virally encoded polymerases, such as RNA-dependent RNA polymerase (RdRp) or reverse transcriptase for viruses with RNA genomes or retroviruses, respectively after the viral genome is introduced into the host cell. The virus suppresses or activates host cellular pathways destructive or beneficial to the host cell's survival to ensure optimal replication. Human immunodeficiency virus (HIV) propagation necessitates viral enzymes such as reverse transcriptase, integrase, protease and Tat, a transcription trans-activator. Curcumin was found to inhibit HIV-integrase and protease through direct intermolecular binding.

According to docking studies, curcumin interacts with HIV protease and integrase active sites [59]. The concurrent occupation of two binding sites in the viral protease in-

creases curcumin activity aided by coordinating central keto-enol groups of two curcumin to a boron atom [60]. Curcumin's core seven-carbon chain has an enone group that acts as a Michael acceptor electrophile (MAE), allowing it to conjugate with other proteins via Michael addition. Treatment with several natural products with electrophilic properties, such as curcumin, rosmarinic acid, gambogic acid, celastrol and ferulic acid, can inhibit 55% of Tat-dependent transcription of HIV [61]. Curcumin influences viral replication via modifying cellular parameters and directly targeting the viral replication machinery. Curcumin's MAE characteristics disrupt Tat function during HIV infection [61]; nevertheless, it also postulated an additional method. Curcumin therapy lowered Tat protein levels, Tat-mediated LTR promoter transactivation, and HIV-1 virion generation in cells transiently expressing Tat [62]. Curcumin appears to have reduced Tat protein accumulation by increasing Tat protein degradation rate via the cellular proteasomal pathway rather than speeding up mRNA degradation.

4.4. Curcumin Suppresses Intercellular Signaling Cascades

The viral infection damages the cell as it competes with the host cell for its cellular apparatus. For their advantage, survival and replication could hijack various intracellular signalling cascades such as NF-κB, PI3K/Akt, MAPK signalling pathways and the ubiquitin protease system (UPS). Accumulated evidence indicates curcumin mediates antiviral effects partly by modulating multiple cell signalling pathways and essential cellular processing.

4.5. Attenuation of PI3K/Akt and NF-κB Signalling Pathways

Akt has many functions; it phosphorylates downstream substrates that activate various cellular processes such as translation, RNA processing, apoptosis and autophagy [63,64]. Phosphatidylinositol-3-kinase phosphorylates and activates AKT (PI3K). Many viruses rely on the PI3K/Akt pathway to replicate by activating it. The AKT pathway is required for HCV development and replication. Curcumin decreased HCV replication by decreasing the Akt pathway, suppressing the transcriptional factor sterol regulatory element-binding protein-1 (SREBP-1) required for HCV replication [65]. Activation of the PI3K-Akt pathway increases the expression of heme oxygenase-1 (HO-1) in cells, an enzyme that protects cells from oxidative damage [66]. Aside from the PI3K-Akt pathway, the virus uses a different signalling mechanism. NF-B, in particular, plays a double-edged role in cell survival and cancer development: its effectors target and destroy altered cells, while over-expression can harm cells [66]. Although activation of NF-B leads to the upregulation of multiple antiviral genes, it is essential for the infection of some viruses; for example, the influenza virus directs antiviral activity toward a proviral component for efficient reproduction [66]. Activation of the NF-κB cascade is mediated by the core element IKK kinase complex, which constitutes two kinases, IKKα and IKKβ. By associating with the IKK-β2 complex and interfering with its function, curcumin effectively inhibits the Rift Valley fever virus (RVFV) [51,61]. It was established that curcumin treatment inhibits the kinase activity of the IKK-β2 complex, which leads to down-regulation of viral NSs protein phosphorylation and alteration of cell cycle regulation in RVFV infected cells [48,51].

4.6. Prevent Assembly or Release of New Infectious Virions

The virus life cycle completes inside invaded host cells by reproducing its copies due to its simple body containing nucleic acid (RNA or DNA) and a protein coat. Once a virus attaches to a cell, it finds a way to penetrate, especially through an active site or as cargo in the extracellular particles. Once inside, it removes its protein coat, replicates, assembles, and releases. The virus attaches itself to a host cell during attachment and penetration and injects its genetic material into it. Assembly is the last step in the viral life cycle, whereby all essential components of a viron are collected together to form a basic virus structure before being released [67]. Whether by self-assembly, scaffolding protein-assisted assembly, or viral genome-assisted assembly, morphogenetic reactions involving protein–protein associations and interactions between the viral genome and capsid proteins occur in this

step [68]. However, potential antiviral medication, including turmeric, can destroy post-transcriptionally modified materials, denature viral proteins, and affect the replicated viral genome, thus ending the complete life cycle of a virus. Yet, destroying a virus within a cell requires high sensitivity and selectivity to reduce risks and effects on the host cells.

4.7. Synergistic Effect

Studies revealed that MAC effectively inhibited influenza virus infection (IAV) to a similar, if not superior, extent as curcumin. Both compounds mildly reduced viral NA activity. Surprisingly, unlike Cur, the MAC inhibition of IAV did not occur through blocking HA activity [69]. However, MAC strongly dampened Akt phosphorylation, the prerequisite signalling for efficient IAV propagation. A stronger inhibition effect on IAV infection was observed when MAC treatment was combined with Cur [69]. Collectively, MAC demonstrated clear antiviral activity and likely inhibited IAV via multiple mechanisms that were not identical to Cur. Importantly, Cur and MAC synergistically inhibited IAV infection [69].

4.8. Inhibition of Cell Binding

Curcumin inhibited the encapsulated viruses' ability to bind to cells in a dose-dependent manner while maintaining the integrity of the viral RNA. The time-of-addition experiments with CVB3, CHIKV and ZIKV were used to understand how curcumin could affect viral replication [49]. About 5 mM curcumin was used to treat HeLa cells before and after infection. Viral titres were determined 48 h after infection at MOI 0.1 with CHIKV and ZIKV, or 24 h after infection with infection CVB3, after several rounds of viral replication [49]. Both ZIKV and CHIKV were sensitive to curcumin, even when treatment was initiated after infection; however, treatment was most effective before or at the time of infection. This means the traditional use of curcumin in meals is significant for treating medical conditions [49]. The effect of time of addition of curcumin did not significantly impact CVB3 replication [49], suggesting that curcumin's antiviral effect is early in infection, potentially before the onset of viral replication. Mechanistically, cAgNPs could prevent RSV from infecting the host cells by directly activating the virus, demonstrating that cAgNPs are a promising efficient virucide for RSV [70].

4.9. Improvement of Antiviral Activity of Curcumin

Curcumin's use as traditional medicine resulted from a wide range of antimicrobial properties, such as antiviral properties. Despite the promising potential, curcumin-based drug development is hindered by its poor solubility and cell uptake. Commonly, curcumin is used with other natural compounds to enhance the oral bioavailability of curcumin [71]. The ability of piperine, the main active compound found in black and long peppers (*Pipper nigrum* L. and *Piper longum* L.), inhibits the glucuronidation of many drugs and improves curcumin bioavailability utilised to improve the bioavailability of curcumin [72]. In this case, the number of curcumin finished products are mixed with piperine or black or long pepper to make these products more attractive to consumers. Recently, different techniques have been utilized to improve curcumin antiviral activity, such as preparing curcumin carbon quantum dots and nanocomposites.

A study by Lin and colleagues revealed that curcumin possesses insignificant inhibitory activity (half-maximal effective concentration (EC50) > 200 $\mu g \cdot mL^{-1}$) against EV71 infection in RD cells, but carbon quantum dots derived from curcumin (Cur-CQDs) exhibited higher cytotoxicity toward RD cells (half-maximal cytotoxic concentration (CC50) 1000-fold lower and >34-fold higher, respectively, than those of curcumin, demonstrating their far superior antiviral capabilities and high biocompatibility that can be utilized for mitigation of diseases [73]. A similar study by Loutfy and colleagues revealed strong binding interactions between protein-ligand complexes that gave scores with NS3 protease, NS5A polymerase and NS5B polymerase of −68.51, −54.52 and −157.63 for CuCs nanocomposite, respectively, and −124.91, −159.02 and −129.16 for curcumin, respectively [74]. Apop-

totic genes' expression revealed the caspase-dependent pathway mechanism [74]. CsNPs and CuCs nanocomposite demonstrated maximum viral entry and replication inhibition, confirmed with HCV core protein expression [74], indicating its ability to mitigate viral diseases. A study by Kharisma and Colleagues studied a mixture of Cryptochlorogenic acid (*Moringa orifera)* and curcumin (*Curcuma longa*) computationally proven as dual inhibitors for antivirals by inhibiting Mpro SARS-CoV-2 and as anti-inflammatory through inhibition of NFKB1 activity [75]. However, the results are merely computational, so they must be validated through wet lab research [75]. Researchers in this field have studied various modifications to curcumin intending to amplify its activities, as presented in Table 2.

Table 2. Describes various modifications done on curcumin-based drugs to improve their activity.

Curcumin Based Drug	Output	Remarks	References
Nanocurcumin was generated by a self-nanoemulsion technique that resulted in a nanoemulsion with uniform distribution of average droplet size of 40.85 ± 0.919 nm.	Nanocurcum prepared exhibited higher cell cytotoxicity than curcumin solution and may be explained by better cell uptake. Nanocurcumin treatment suppressed dengue virus (DENV) growth, although no significant difference was observed compared to the curcumin solution counterpart. Greater virus reduction was observed for DENV-1 and DENV-2.	Synthesized nano curcumin improved curcumin physicochemical properties with potential as an antiviral against DENV	[76]
Curcumin Modified Silver Nanoparticles	Curcumin-modified silver nanoparticles (cAgNPs) exhibit a highly effective inhibitory impact against respiratory syncytial virus (RSV) infection, resulting in a two-order-of-magnitude reduction in viral titres at the 15 AgNP doses tested, with no damage to the host cells.	Uniform and stable curcumin silver nanoparticles (AgNPs) with antiviral properties	[70]
Synthesized curcumin bioconjugates bearing dipeptide, fatty acids and folic acid	The synthesized curcumin bioconjugates have antiviral activities against HSV, VSV, FIPV, PIV-3, RSV and FHV, and di-O-tryptophanyl molecules phenylalanine curcumin (2), di-O-decanoyl curcumin (3), had good results with EC50 0.011 mM and 0.029 mM against VSV and FIPV/FHV, respectively.	The increased antiviral activities against a wide range of viruses	[77]
Synthesized uniform and stable cationic carbon dots (CCM-CDs)	Porcine epidemic diarrhoea virus (PEDV) is used as a coronavirus model. The cationic CCM-CDs treatment could inhibit the proliferation of PEDV compared with the common CDs (EDA-CDs). The CCM-CDs treatment changes the surface protein structure in viruses, thereby inhibiting viral entry, suppressing the synthesis of negative-strand RNA, budding of the virus, and accumulation of reactive oxygen species (ROS) by PEDV. F CCM-CDs treatment was also found to suppress viral replication by stimulating the production of interferon-stimulating genes (ISGs) and pro-inflammatory cytokines.	Development of CCM-CDs as a potential antiviral agent for the treatment of coronavirus infections, including PEDV	[78]
Curcumin, gallium-curcumin, Cu-curcumin	curcumin and its new derivatives have remarkable antiviral effects on HSV-1 in cell culture.	Reduction of HSV-1 replication	[79,80]
Curcumin, curcumin boron complexes		Inhibition of HIV-1 and HIV-2 proteases	[60]
Empty nanoemulsion (NE-V) and the nanoemulsion of curcumin (NE-CUR)	The cell viability assay showed that the empty nanoemulsion (NE-V) and the curcumin nanoemulsion (NE-CUR) had little effect on cell viability compared to control cells. Additionally, we observed that cells irradiated in NE-CUR presence presented 90% of cell death. The apoptosis assay further revealed a significant increase in caspases 3 and 7 in A431 cells expressing both HPV-16 E6 variants after treatment with NE-CUR, indicating a potential antiviral effect.	HPV	[81]

4.10. Potential of Curcumin as Antiviral Agent

Antiviral drugs refer to a group of medications used to treat viral infections. Antivirals that target specific viruses are successful in this scenario, but broad-spectrum antivirals are efficient against many viruses [82,83]. Unlike antibiotics, which kill the infection they fight, antivirals stop viruses from growing. Antiviral medications are one type of antimicrobial, including antibacterial, antifungal, and antiparasitic drugs and monoclonal antibody-based antiviral drugs. Because antivirals are thought to be harmless for the host, they can be utilized to treat infections. Antiviral drug resistance is induced by changes in viral genotypes that reduce drug sensitivity [84,85]. Drugs' effectiveness against the target virus has been reduced or eliminated in this scenario. As resistance has grown to all particular and effective antimicrobials, including antiviral medicines, the problem will undoubtedly remain a major impediment to antiviral therapy. Developing novel antiviral agents presents several challenges and requires significant drug design and validation [86]. Thus, exploring the repurposing of already-approved drugs or natural compounds can provide alternatives to developing novel antivirals [86]. Curcumin, a constituent of turmeric, has been described to have several functions in preventing or treating diseases, including cancers and viral infections [86]. Curcumin has shown antiviral activity over many viruses, as indicated in Table 3.

Table 3. Curcumin has shown antiviral activity over various viruses. Nanoparticles range from 1 to 100 nm and close to 100 nm [87] and are efficient drug delivery systems. Curcumin nanoparticles are reported to range from 2 to 40 nm [88], but usually, size depends on the methodology used for its preparation.

Substance	Antiviral Activity	Virus	References
Curcumin	Decreased regulation of Jun D protein in HTLV-1-infected T-cell lines	HTLV-1	[89]
Curcumin	Inhibition expression of viral oncoproteins of E6 and E7 and Decreased regulation effect on the transcription of HPV-18	HPV	[90,91]
Curcumin	Reduced production of infective viral particles	JEV	[92]
Curcumin	HCV replication decreased by the Akt-SREBP-1 pathway suppression	HVC	[7]
Curcumin	Replication inhibition through UPS dysregulation	Coxsackievirus	[93]
aqueous Curcumin extract	Increasing the p53 level leads to suppression of HBV replication	HBV	[94]
Curcumin	Significant protection against HSV-2 in a mouse model	HSV-2	[95]
Curcumin	Haemagglutination inhibition	Influenza	[96]
Curcumin	Inhibition of HIV-1 LTR-directed gene expression, Inhibition of HIV-1 Integrase and Curcumin, Inhibition of Tat protein acetylation	HIV	[97–99]
Curcumin	Immediate early antigen (IEA) and UL83A expression	Human cytomegalovirus (HCMV)	[100]
Curcumin	BZLF-1 inhibitor	Epstein-Barr virus (EBV)	[101]
Curcumin	Inhibition of viral entry	Bovine herpesvirus 1 (BHV 1)	[102]
Curcumin	Interfered with viral life cycle stages	Human norovirus (HuNoV)	[56]
Curcumin	Virucidal effect (virus inactivation)	Respiratory syncytial virus (RSV)	[56,103]
Curcumin	Viral entry and viral replication	Fish viral haemorrhagic septicaemia virus (VHSV)	[58]
Curcumin	Virucidal effect (attack envelope), inhibition of viral entry, and viral replication	Influenza A virus (IAV)	[48,97]
Curcumin			[54,104]

5. Application of Curcumin

Curcumin's full potential is hampered by poor oral bioavailability and insufficient solubility in aqueous solvents, which result in poor absorption, rapid metabolism and rapid systemic elimination. Curcumin microcapsules with improved solubility are suitable for use as a preservative and colourant in the food industry, with MIC values ranging from 15.7 to 250 g/mL against food-borne pathogens such as *Penicillium notatum*, *Saccharomyces cerevisiae*, *Yersinia enterocolitica*, *B. cereus*, *E. coli*, *Staph. aureus* and *B. subtilis* [105]. With the need to maintain the performance and health of birds, there is increased interest in creating natural alternatives to antibiotic growth promoters. Over the last decade, turmeric has been widely employed in chicken diets [106]. For decades curcumin has been utilized to mitigate various medical conditions and recently to mitigate COVID-19. According to the literature, curcumin is a promising preventative and therapeutic candidate for COVID-19 [54]. Curcumin's antiviral effect against various enveloped viruses, including SARS-CoV-2, is aided by many mechanisms: direct contact with viral membrane proteins; breakdown of the viral envelope; inhibition of viral proteases and induction of host antiviral responses [54]. Curcumin has been publicised to be safe and well-tolerated in healthy and ill humans and protects against deadly pneumonia and acute respiratory distress syndrome (ARDS) by inhibiting the pathways NF-B, inflammasome, IL-6 trans signal, and HMGB1 [105], indicating its future use as a preventive treatment in clinical and public health settings.

5.1. Traditional Uses and Ethnopharmacology of Curcumin

Curcuma longa is an important nutritional plant with antioxidant, antibacterial, anti-inflammatory, anticancer and anti-clotting properties [6,107]. Alternative therapeutic options such as medicinal plants have a long history of treating many diseases, and it is widely known that herbs are a good source of possible therapeutic chemicals [2,6,108]. Turmeric (*Curcuma longa*) has been used as a spice in daily cooking and traditional medicine for over 6000 years. *C. longa* is a South and Southeast Asian plant rhizome found in Pakistan, China, Indonesia, India, Nepal, Jamaica, Bangladesh, Malaysia, El Salvador, Taiwan and Haiti. Curcuma is a genus of medicinal plants with therapeutic properties that include about 70 identified species [6,72,108–110]. They have long been employed as food preservatives, colouring pigments and spices and have great therapeutic potential. *Curcuma longa* plant belongs to Zingiberaceae (ginger) family widely grown in Southeast Asia, primarily in China and India [3,5,111,112].

5.2. Application of Curcumin-Based Nano-Formulations

Curcumin-based nano-formulations have a promising future in preventing, diagnosing, and treating medical disorders such as cancer, but further research is needed to determine the safety and delivery strategy [113–115]. Efficient curcumin delivery via nanotechnology helps overcome issues with solubility, rapid drug metabolism, degradation, and drug stability. It should also diffuse or target indent tissues while minimizing unintended toxicity to surrounding normal cells/tissues [113–116]. For example search for more effective cancer treatment with fewer side effects is ongoing; curcumin has demonstrated potential anticancer activities through numerous pathways, including inhibiting and/or inducing the generation of multiple cytokines, interfering with multiple cellular mechanisms, enzymes, or growth factors including IκB kinase β (IκKβ), tumour necrosis factor-alpha (TNF-α), signal transducer, and activator of transcription 3 (STAT3), cyclooxygenase II (COX-2), protein kinase D1 (PKD1), nuclear factor-kappa B (NF-κB), epidermal growth factor, and mitogen-activated protein kinase (MAPK) [117], indicating that curcumin nano formulations may have potential applications. Ahmed and colleagues synthesized and characterized the curcumin-loaded AgNPs based on the size, polydispersity index, potential, morphology, size distribution, drug loading effectiveness and interactions with excipients. The anti-cancer potentials of the nanoparticles were evaluated against MM-138, FM-55 and MCF-7 cell lines. The nanoparticles effectively transported a greater amount

of curcumin, indicating that it is a superb nanocarrier. In addition, the curcumin-loaded nanoparticles effectively fought against three different cancerous cell lines: MM-138, FM-55 and MCF-7. The potential of curcumin-based drugs, including nano formulations, is yet to be utilized to manage communicable and non-communicable diseases [117,118].

Haghnegahdar and colleagues fabricated CM-functionalized nanocomposite with a large surface area, extended stability, strong adaptation, anti-interference capability and considerable reproducibility [119]. The fabricated nanocomposite exhibits a strong electrocatalytic activity toward the oxidation of analytes, especially for dopamine (DA) (vs. Ag/AgCl), according to the electrochemical data. While the DA, uric acid (UA) and guanine (GU) results are consistent, there was no equivalent electrochemical peak for ascorbic acid (AA) [119]. It was further reported for DA, GU and UA, respectively, that their calibration curves were linear in the ranges of 12.0–200.0, 16.0–400.0, and 18–650.0 mol/L and the detection limits for DA, GU, and UA values were 0.14 mol/L, 0.19 mol/L and 0.38 mol/L, respectively [119]. The produced electrode was effectively used for the simultaneous analysis of analytes in samples of blood, serum, urine and dopadic ampoules [119]. The electrode had a lower detection limit, indicating its potential application for the detection of disease biomarkers as may be present at lower concentrations. This may be helpful in the early detection of diseases and hence their early mitigation.

Results of a study by Proença-Assunção and colleagues revealed that without metabolic activation, Cur-AgNPs are not mutagenic, but when exposed to S9, Cur-AgNPs become mutagenic to the TA98 and TA100 strains, demonstrating the importance of metabolizer enzymes to activate Cur-AgNPs on these bacteria, which regained their capacity to synthesize histidine (His+). The curcumin-based nanoparticles may be a potential drug for managing medical disorders. The possibility of engineering nano-formulations to multifunctionality, merging therapeutic, targeting and diagnostic features, has shown potential advancement in managing diseases globally. These potentials caused the nanoparticles to rise as therapeutic agents with increased efficacy and diminished systemic drug side effects helpful for managing chronic diseases.

5.3. Electrostatic Nature and Size of Curcumin-Based Nano-Formulations

Electrostatic forces are among the most versatile interactions for mediating nanostructured material assembly [117,119–128]. These forces can be long or short-ranged, attractive or repulsive, and the shapes of the charged nano-objects can control their directionality, depending on the experimental conditions [117,120–122]. Electrostatic interactions operate in nano-formulations such as electroactive and or switchable nanoparticles, charged nanoparticle mixtures, nanoparticle chains, sheets, coatings, crystals, crystals-within-crystals, and other structures used in chemical sensing and amplification [123,125,126,128–132]. On the other hand, the nano-formulations charge can be used to arrange nanoparticles to higher-order structures, but it is necessary to utilize oppositely charged nanoparticles [123,125,126,129–132]. The electrostatic repulsion is the potential for the increased surface activity of nanoparticles, drug delivery, and formation of static and dynamic structures [123,125,126,129–132], which are necessary to diagnose and mitigate medical conditions. Nano particles range from 1 to 100 nm and close to 100 nm [87] and are efficient drug delivery systems. Curcumin nanoparticles are reported to range from 2 to 40 nm [88], but usually their size depends on the methodology used for their preparation. The size of a particle influences the overall charge density of a particle. Smaller size creates larger charge density for molecules with the same charge but differing size. A study by Vatanparast and colleagues investigated the role of electrostatic interactions in improving surface properties of anionic surfactants in silica nanoparticles [130]. Results indicated that the observed SDS interfacial behaviour in the presence of nanoparticles was due to the electrostatic repulsive interaction [130], leading to the increased surfactant surface activity and the adsorption of the dodecanol on the surfaces of particles, affecting the adsorption dynamic and resulting in faster interfacial relaxation, indicating the potential of the electrostatic interactions in the functioning of nano-formulations.

5.4. Curcumin Therapy for Mitigation of COVID-19

Coronavirus disease (COVID-19) is a virus-borne infection caused by the SARS-CoV-2 virus. Most people infected with the virus will have mild to moderate respiratory illness and recover without special treatment [133–135]. Some, however, will become critically ill and require medical attention. People over 65 and those with underlying medical conditions such as cardiovascular disease, diabetes, chronic respiratory disease or cancer are at a higher risk of developing a serious illness. Any age can become seriously ill or die due to COVID-19 [104,134,136,137]. Curcumin is an effective molecule for treating viral infections due to its ability to modulate various molecular targets involved in the infection process [134,138–141]. These processes include inactivation and attack on virus structures [138,140], inhibition of virus attachment and entry into cells [104,134,136,137], protease inhibition [104,134,136,137], and transcription and replication regulation [104,134,136,137]. These factors led to the wide application of curcumin during the era of COVID-19 pandemic in the clinical setting [135,140–147]. Curcumin therapy decreased symptoms, hospitalisation duration and death [104,136,139,142,145,147–150].

In a recent study, Kow and colleagues reported significantly reduced odds of mortality with the use of curcumin relative to the non-use of curcumin in patients with COVID-19, indicating the potential use of cumin for mitigation of the pandemic [136]. Bormann and colleagues reported that turmeric root extract, dissolved turmeric capsule and pure curcumin effectively neutralized SARS-CoV-2 in Vero E6 and human Calu- 3 cells at subtoxic levels concentrations [151]. It was further observed that curcumin significantly reduced SARS-CoV-2 RNA levels in cell culture, indicating it is a promising complementary COVID-19 treatment [146,151–153]. In this case, curcumin, turmeric root or capsules may be used to manage COVID-19. Therefore, studies are needed to potentially investigate further curcumin-based drugs for managing COVID-19 and future pandemic.

5.5. User Preference for Curcumin

Turmeric has been widely used for various applications globally since the prehistoric period. However, literature is silent about user preference for this precious herb. All aspects of turmeric are widely reviewed, such as medical use due to potential pharmacological activities, inclusion in daily diet, and its use as a preservative. Future research should cover information on user preference apart from its acceptability due to its potential.

5.6. Safety Aspects of Curcumin

Curcumin is the chief bioactive compound in turmeric, one of the most effective nutritional supplements and traditional medicine [154]. Studies demonstrated that curcumin has anti-inflammatory, anti-oxidant and anti-neoplastic properties. Previous literature has described the potential roles of this phytochemical in treating and preventing specific diseases such as metabolic syndrome, arthritis, anxiety, hyperlipidaemia and cancers [155–157]. The US FDA recognised turmeric as safe and granted an acceptable daily intake (ADI) level of 3 mg/kg-BW by the joint FAO and WHO Expert Committee on Food Additives in 1996 [10]. Despite enthusiasm for the potential value of curcumin on human health that has led to more than 120 clinical trials of curcuminoids, efforts in curcumin-based drug development have been hampered by certain obstacles, including its poor bioavailability, which is primarily due to poor absorption and metabolic instability, and enigmatic diverse effects (or promiscuous bioassay profile) that leads to speculation of curcumin being a pan-assay interference compound (PAINS) [22]. The poor bioavailability issue has led to numerous efforts to improve bioavailability, such as modulation of route and medium of curcumin administration, blocking of metabolic pathways by concomitant administration with other agents, conjugation and structural modifications of curcumin [158].

Alafiatayo and colleagues embryotoxicity and teratogenic effects of *Curcuma longa* extract on zebrafish (*Danio rerio*) [159]. Results indicated that the toxicity effects were reliant on a dose, while, at 125.0 µg/mL, mortality of embryos was observed, and physical body deformities of larvae were recorded among the hatched embryos at higher concentrations.

The teratogenic effects of the extract were severe at higher doses leading to physical body deformities such as bend trunk, enlarged yolk sac oedema and kink tail [159]. Lastly, the therapeutic index (TI) values were roughly identical for different doses investigated. The results revealed that plants with therapeutic potential could also threaten when consumed at higher doses, especially in the embryos [159]. Thus, detailed toxicity analysis should be conducted on medicinal plants to ascertain their safety on the embryos and their development. A phase 1 human trial consisting of 25 clients administered up to 8000 mg of curcumin per day for 3 months revealed no toxicity from curcumin [157,160].

Similarly, five other trials using 1125–2500 mg of curcumin daily have also found it safe for consumption [161–166]. These human trials have found some evidence of the anti-inflammatory activity of curcumin. The laboratory studies have identified several different molecules involved in inflammation that is inhibited by curcumin, including phospholipase, lipooxygenase, cyclooxygenase 2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein, tumour necrosis factor (TNF) and interleukin-12 (IL-12) [161–166]. It may exert anti-inflammatory activity by inhibiting several different molecules that play a role in inflammation [33,48,94,96,97,102,103], indicating potential medical applicability.

5.7. Availability of Finished Products

Root and rhizome of the turmeric plant (*Curcuma longa* L.) are of high therapeutic and economic potential globally, mainly used as a food and supplement. Reports of finished products made of turmeric are available [167]. It was reported that quality differences were observed, which may interfere with its use in clinical settings [167]. Therefore, establishing and managing integrated systems for dietary supplements quality monitoring throughout the supply chain from seed to finished product is essential. Booker and colleagues evaluated turmeric finished products, which were formulated in tablets (2), powder (1), extracts (2), soft gels (2) and capsules (43) which contained either plant extract or crude ground material of the plant or a combination of plant extract and crude ground material [167]. This indicates the availability of finished products in the various formulations. Table 4 details the application of *Curcuma longa*.

Table 4. Application of Turmeric (*Curcuma longa*).

Purpose of Usage	Remarks	References
Curcumin is used in the mitigation of inflammatory disorders	This is due to its ability to inhibit different molecules involved in inflammation, such as lipooxygenase, COX-2, interferon-inducible protein, and tumour necrosis factor	[157]
Used in the management of diabetes mellitus:	Turmeric rhizome powder is very useful with amla juice and honey in Madhumeha (diabetes mellitus)	[109,157]
Used in the mitigation of cardiovascular disorders	This is contributed by the ability of the antioxidants in turmeric to prevent damage to cholesterol, hence its protection against atherosclerosis.	[110]
Used in the mitigation of allergic activity	This is due to the ability of curcumin to inhibit nonspecific and specific mast cell-dependent allergic reactions.	[168]
Used in the mitigation of dermatophytic activity:	Rhizomes of Haridra fresh juice have the antiparasitic ability in numerous skin affections.	[4]
Used in mitigation of drug resistance:	This is due to the ability of curcumin as a potent drug resistance preventer.	[169]
Used as additives in other drugs	This is due to the synergism of Curcumin and other drugs.	[110]
Used in the management of jaundice (Hepatoprotective)	Due to the synergistic interaction of the rhizome with amla juice and other substances.	[110,170]
Used in mitigation of ischemic brain injury	This is attributed to Curcuma oil's neuroprotective action, which reduces the negative effects of ischemia by reducing nitrosative and oxidative stress.	[171]

Table 4. *Cont.*

Purpose of Usage	Remarks	References
Used for mitigation of respiratory disorders	The rhizome is used for gargling, and the piece of the rhizome is slightly burnt and given for chewing.	[4]
Gastrointestinal disorders:	This is due to the anthelmintic activity of the fresh juice of Haridra.	[172]
Used as an additive in poultry diet	Used as a natural growth promoter and disease control.	[106,173]
Used for management of Alzheimer's disease	This is due to the ability of curcumin to reduce oxidative damage and reverse the amyloid pathology.	[107]
Used for chemoprotection In tumour cells or tissue	Curcumin is nutraceutical. Chemopreventive ability.	[174]
Used in mitigation of cancer	Curcumin possesses anticancer activities via its effect on diverse biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis and metastasis.	[175]

6. Conclusions and Recommendations

Curcumin plays a multipotent role against bacteria, fungi and viruses. Its synergistic effects like anti-oxidant, anti-inflammatory, and anti-tumoral activities have made it a miracle drug. Their ability to affect various molecular targets makes them a potential candidate for preventing and treating several diseases. Many potentials are seen in curcumin-enhanced drugs that can be readily bioavailable with targeted effects against viruses. The effectiveness of curcumin in treating infectious diseases is hindered by its solubility; different techniques have been observed to improve its effectiveness and hence the possibility of its use in medicine. There is the potential to utilize the antiviral role of curcumin against new and emerging viruses. Conversion of curcumin to bioconjugates, nanoemulsion, nanoparticles and nanotubes is observed to improve its activity, increasing its medical application. Similarly, curcumin is observed to work best in treatments if it is initiated early, indicating the need to re-motivate its use in preventive medicine in daily meals to aid in protecting the human body from contracting an infection from various pathogenic organisms such as viruses.

Author Contributions: Ideation and conceptualization, A.S.R., H.M.M. and B.B.L.S.; methodology and first draft, A.S.R. and H.M.M.; final draft scrutiny and reference management, A.S.R.; English language structure and grammar check, H.M.M. and B.B.L.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was facilitated by University of Dodoma research fund for Manuscript processing and publication. The statements and opinion in this paper are solely the responsibility of the authors, and do not necessarily represent the views of the University of Dodoma (UDOM) or its research commetee.

Informed Consent Statement: Not applicable.

Data Availability Statement: This study utilized secondary data and is referenced within the article.

Acknowledgments: Aurthors of this manuscript acknowledges the contribution of anonymous reviewers who critically reviewed this work, their feedbacks and critics improved the quality of the work. The University of Dodoma and its research commetee are equally acknowledged.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hussain, Z.; Thu, H.E.; Amjad, M.W.; Hussain, F.; Ahmed, T.A.; Khan, S. Exploring recent developments to improve antioxidant, anti-inflammatory and antimicrobial efficacy of curcumin: A review of new trends and future perspectives. *Mater. Sci. Eng. C* **2017**, *77*, 1316–1326.
2. Hussain, W.; Haleem, K.S.; Khan, I.; Tauseef, I.; Qayyum, S.; Ahmed, B.; Riaz, M.N. Medicinal plants: A repository of antiviral metabolites. *Future Virol.* **2017**, *12*, 299–308.
3. Krishnaswamy, K. Traditional Indian spices and their health significance. *Asia Pac. J. Clin. Nutr.* **2008**, *17*, 265–268. [PubMed]
4. Pandey, G. *Dravyaguna Vijnana*, 2nd ed.; Krishnadas Academy Publisher: Varanasi, India, 2002; Volume 1, pp. 737–746.
5. Prasad, S.; Aggarwal, B.B. Turmeric, the golden spice. In *Herbal Medicine: Biomolecular and Clinical Aspects*, 2nd ed.; CRC Press: Boca Raton, FL, USA, 2011.
6. Kapoor, S.; Lata Saraf, S. Topical Herbal Therapies an Alternative and Complementary Choice. *Res. J. Med. Plant* **2011**, *5*, 650–669.
7. Zorofchian Moghadamtousi, S.; Abdul Kadir, H.; Hassandarvish, P.; Tajik, H.; Abubakar, S.; Zandi, K. A Review on Antibacterial, Antiviral, and Antifungal Activity of Curcumin. *BioMed Res. Int.* **2014**, *2014*, 186864. [CrossRef]
8. Ody, P. *Turmeric: Nature's Miracle Healer: Fact or Fiction*; Souvenir Press: London, UK, 2018.
9. Mathew, A.; Pushpanath, S. *Indian Spices*; Dee Bee Info Publications: Kottayam, India, 2005.
10. Institute, N.C. Clinical development plan: Curcumin. *Cell. Biochem.* **1996**, *26*, 72–85.
11. Sasikumar, B. Genetic resources of Curcuma: Diversity, characterization and utilization. *Plant Genet. Resour.* **2005**, *3*, 230–251.
12. Easmin, M.S.; Sarker, M.Z.; Ferdosh, S.; Shamsudin, S.H.; Yunus, K.B.; Uddin, M.S.; Sarker, M.M.R.; Akanda, M.J.H.; Hossain, M.S.; Khalil, H.A. Bioactive compounds and advanced processing technology: Phaleria macrocarpa (sheff.) Boerl, a review. *J. Chem. Technol. Biotechnol.* **2015**, *90*, 981–991.
13. Van Andel, T.; Carvalheiro, L.G.; Medicine, A. Why urban citizens in developing countries use traditional medicines: The case of Suriname. Evid.-Based Complement. *Altern. Med.* **2013**, *2013*, 1–13.
14. Kew Science. *Curcuma longa* L. Plants of the World Online. Available online: https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:796451-1 (accessed on 19 June 2022).
15. Kandiannan, K.; Anandaraj, M.; Prasath, D.; Zachariah, T.J.; Krishnamurthy, K.; Srinivasan, V. Evaluation of short and tall true turmeric (*Curcuma longa*) varieties for growth, yield and stability. *Indian J. Agric. Sci.* **2015**, *85*, 718–720.
16. Nair, R.R.; Shiva, K.N.; Anchu, S.; Zachariah, T.J. Characterization of open-pollinated seedling progenies of turmeric (*Curcuma longa* L.) based on chromosome number, plant morphology, rhizome yield and rhizome quality. *Cytologia* **2010**, *75*, 443–449. [CrossRef]
17. Kim, S.; Ko, S.-C.; Kim, Y.-S.; Ha, S.-K.; Park, H.-Y.; Park, Y.; Lee, S.-H. Determination of *Curcuma longa* L.(Turmeric) leaf extraction conditions using response surface methodology to optimize extraction yield and antioxidant content. *J. Food Qual.* **2019**, *2019*, 1–8.
18. Kumar, A.; Singh, M.; Singh, P.P.; Singh, S.K.; Raj, P.; Pandey, K.D. Antioxidant efficacy and curcumin content of turmeric (*Curcuma-longa* L.) flower. *Int. J. Curr. Pharm. Res.* **2016**, *8*, 112–114.
19. Fujisawa, S.; Murakami, Y. Eugenol and its role in chronic diseases. *Drug Discov. Mother Nat.* **2016**, *929*, 45–66.
20. Khopde, S.M.; Indira Priyadarsini, K.; Palit, D.K.; Mukherjee, T. Effect of Solvent on the Excited-state Photophysical Properties of Curcumin. *Photochem. Photobiol.* **2000**, *72*, 625–631. [CrossRef]
21. Jackson, P.A.; Widen, J.C.; Harki, D.A.; Brummond, K.M. Covalent Modifiers: A Chemical Perspective on the Reactivity of α,β-Unsaturated Carbonyls with Thiols via Hetero-Michael Addition Reactions. *J. Med. Chem.* **2017**, *60*, 839–885. [CrossRef]
22. Nelson, K.M.; Dahlin, J.L.; Bisson, J.; Graham, J.; Pauli, G.F.; Walters, M.A. The essential medicinal chemistry of curcumin: Miniperspective. *J. Med. Chem.* **2017**, *60*, 1620–1637.
23. Baker, M. Deceptive curcumin offers cautionary tale for chemists. *Nature* **2017**, *541*, 144–145.
24. Bisson, J.; McAlpine, J.B.; Friesen, J.B.; Chen, S.-N.; Graham, J.; Pauli, G.F. Can invalid bioactives undermine natural product-based drug discovery? *J. Med. Chem.* **2016**, *59*, 1671–1690. [CrossRef]
25. He, Y.; Li, W.; Hu, G.; Sun, H.; Kong, Q. Bioactivities of EF24, a novel curcumin analog: A review. *Front. Oncol.* **2018**, *8*, 614.
26. Metzler, M.; Pfeiffer, E.; Schulz, S.I.; Dempe, J.S. Curcumin uptake and metabolism. *BioFactors* **2013**, *39*, 14–20. [CrossRef] [PubMed]
27. Goel, A.; Kunnumakkara, A.B.; Aggarwal, B.B. Curcumin as "Curecumin": From kitchen to clinic. *Biochem. Pharmacol.* **2008**, *75*, 787–809. [CrossRef] [PubMed]
28. Araújo, C.C.; Leon, L.L. Biological activities of *Curcuma longa* L. *Mem. Inst. Oswaldo Cruz* **2001**, *96*, 723–728. [CrossRef] [PubMed]
29. De, R.; Kundu, P.; Swarnakar, S.; Ramamurthy, T.; Chowdhury, A.; Nair, G.B.; Mukhopadhyay, A.K. Antimicrobial activity of curcumin against Helicobacter pylori isolates from India and during infections in mice. *Antimicrob. Agents Chemother.* **2009**, *53*, 1592–1597. [CrossRef]
30. Santezi, C.; Reina, B.D.; de Annunzio, S.R.; Calixto, G.; Chorilli, M.; Dovigo, L.N. Photodynamic potential of curcumin in bioadhesive formulations: Optical characteristics and antimicrobial effect against biofilms. *Photodiagnosis Photodyn. Ther.* **2021**, *35*, 102416. [CrossRef]
31. Hussain, Y.; Alam, W.; Ullah, H.; Dacrema, M.; Daglia, M.; Khan, H.; Arciola, C.R. Antimicrobial Potential of Curcumin: Therapeutic Potential and Challenges to Clinical Applications. *Antibiotics* **2022**, *11*, 322. [CrossRef]
32. Brouet, I.; Ohshima, H. Curcumin, an anti-tumor promoter and anti-inflammatory agent, inhibits induction of nitric oxide synthase in activated macrophages. *Biochem. Biophys. Res. Commun.* **1995**, *206*, 533–540. [CrossRef]

33. Sreejayan, N.; Rao, M.; Priyadarsini, K.; Devasagayam, T. Inhibition of radiation-induced lipid peroxidation by curcumin. *Int. J. Pharm.* **1997**, *151*, 127–130. [CrossRef]
34. Anand, P.; Kunnumakkara, A.B.; Newman, R.A.; Aggarwal, B.B. Bioavailability of curcumin: Problems and promises. *Mol. Pharm.* **2007**, *4*, 807–818. [CrossRef]
35. Maheshwari, R.K.; Singh, A.K.; Gaddipati, J.; Srimal, R.C. Multiple biological activities of curcumin: A short review. *Life Sci.* **2006**, *78*, 2081–2087. [CrossRef]
36. Goel, G.; Makkar, H.P.; Francis, G.; Becker, K. Phorbol esters: Structure, biological activity, and toxicity in animals. *Int. J. Toxicol.* **2007**, *26*, 279–288. [CrossRef] [PubMed]
37. Kumar, A.; Dhawan, S.; Hardegen, N.J.; Aggarwal, B.B. Curcumin (diferuloylmethane) inhibition of tumor necrosis factor (TNF)-mediated adhesion of monocytes to endothelial cells by suppression of cell surface expression of adhesion molecules and of nuclear factor-κB activation. *Biochem. Pharmacol.* **1998**, *55*, 775–783. [CrossRef]
38. Bharti, A.C.; Donato, N.; Singh, S.; Aggarwal, B.B. Curcumin (diferuloylmethane) down-regulates the constitutive activation of nuclear factor–κB and IκBα kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. *Blood J. Am. Soc. Hematol.* **2003**, *101*, 1053–1062. [CrossRef] [PubMed]
39. Aggarwal, B.B.; Bhardwaj, A.; Aggarwal, R.S.; Seeram, N.P.; Shishodia, S.; Takada, Y. Role of resveratrol in prevention and therapy of cancer: Preclinical and clinical studies. *Anticancer. Res.* **2004**, *24*, 2783–2840.
40. Malkin, E.Z.; Bratman, S.V. Bioactive DNA from extracellular vesicles and particles. *Cell Death Dis.* **2020**, *11*, 584. [CrossRef]
41. Lam, J.H.; Smith, F.L.; Baumgarth, N. B cell activation and response regulation during viral infections. *Viral Immunol.* **2020**, *33*, 294–306. [CrossRef]
42. Gao, Y.; Wijewardhana, C.; Mann, J.F. Virus-like particle, liposome, and polymeric particle-based vaccines against HIV-1. *Front. Immunol.* **2018**, *9*, 345. [CrossRef]
43. Bello-Morales, R.; Ripa, I.; López-Guerrero, J.A. Extracellular vesicles in viral spread and antiviral response. *Viruses* **2020**, *12*, 623. [CrossRef]
44. Magwa, M.L.; Gundidza, M.; Gweru, N.; Humphrey, G. Chemical composition and biological activities of essential oil from the leaves of Sesuvium portulacastrum. *J. Ethnopharmacol.* **2006**, *103*, 85–89. [CrossRef]
45. Dosoky, N.S.; Setzer, W.N. Chemical composition and biological activities of essential oils of Curcuma species. *Nutrients* **2018**, *10*, 1196. [CrossRef]
46. Liu, Z.; Ying, Y. The inhibitory effect of curcumin on virus-induced cytokine storm and its potential use in the associated severe pneumonia. *J. Front. Cell Dev. Biol.* **2020**, *8*, 479. [CrossRef]
47. Yang, L.; Li, J.; Li, S.; Dang, W.; Xin, S.; Long, S.; Zhang, W.; Cao, P.; Lu, J. Extracellular Vesicles Regulated by Viruses and Antiviral Strategies. *Front. Cell Dev. Biol.* **2021**, *9*, 2842. [CrossRef] [PubMed]
48. Chen, T.-Y.; Chen, D.-Y.; Wen, H.-W.; Ou, J.-L.; Chiou, S.-S.; Chen, J.-M.; Wong, M.-L.; Hsu, W.-L. Inhibition of enveloped viruses infectivity by curcumin. *PLoS ONE* **2013**, *8*, e62482. [CrossRef] [PubMed]
49. Mounce, B.C.; Cesaro, T.; Carrau, L.; Vallet, T.; Vignuzzi, M. Curcumin inhibits Zika and chikungunya virus infection by inhibiting cell binding. *Antivir. Res.* **2017**, *142*, 148–157. [CrossRef] [PubMed]
50. Vivcharenko, V.; Przekora, A. Modifications of wound dressings with bioactive agents to achieve improved pro-healing properties. *Appl. Sci.* **2021**, *11*, 4114. [CrossRef]
51. Mathew, D.; Hsu, W.-L. Antiviral potential of curcumin. *J. Funct. Foods* **2018**, *40*, 692–699. [CrossRef]
52. Zhang, X.; Chen, L.; Hu, C.; Fast, D.; Zhang, L.; Yang, B.; Kan, J.; Du, J. Curcumin attenuates poly (I: C)-induced immune and inflammatory responses in mouse macrophages by inhibiting TLR3/TBK1/IFNB cascade. *J. Funct. Foods* **2022**, *89*, 104949. [CrossRef]
53. Pécheur, E.-I. Curcumin against hepatitis C virus infection: Spicing up antiviral therapies with 'nutraceuticals'? *Gut* **2014**, *63*, 1035–1037. [CrossRef]
54. Thimmulappa, R.K.; Mudnakudu-Nagaraju, K.K.; Shivamallu, C.; Subramaniam, K.T.; Radhakrishnan, A.; Bhojraj, S.; Kuppusamy, G.J.H. Antiviral and immunomodulatory activity of curcumin: A case for prophylactic therapy for COVID-19. *Heliyon* **2021**, *7*, e06350. [CrossRef]
55. Aggarwal, B.B.; Deb, L.; Prasad, S.J.M. Curcumin differs from tetrahydrocurcumin for molecular targets, signaling pathways and cellular responses. *Molecules* **2014**, *20*, 185–205. [CrossRef]
56. Yang, M.; Lee, G.; Si, J.; Lee, S.-J.; You, H.J.; Ko, G. Curcumin shows antiviral properties against norovirus. *Molecules* **2016**, *21*, 1401. [CrossRef] [PubMed]
57. Ou, J.L.; Mizushina, Y.; Wang, S.Y.; Chuang, D.Y.; Nadar, M.; Hsu, W.L. Structure–activity relationship analysis of curcumin analogues on anti-influenza virus activity. *FEBS J.* **2013**, *280*, 5829–5840. [CrossRef] [PubMed]
58. Jeong, E.-H.; Vaidya, B.; Cho, S.-Y.; Park, M.-A.; Kaewintajuk, K.; Kim, S.R.; Oh, M.-J.; Choi, J.-S.; Kwon, J.; Kim, D. Identification of regulators of the early stage of viral hemorrhagic septicemia virus infection during curcumin treatment. *Fish Shellfish Immunol.* **2015**, *45*, 184–193. [CrossRef] [PubMed]
59. Vajragupta, O.; Boonchoong, P.; Morris, G.M.; Olson, A.J. Active site binding modes of curcumin in HIV-1 protease and integrase. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3364–3368. [CrossRef]
60. Sui, Z.; Salto, R.; Li, J.; Craik, C.; de Montellano, P.R.O. Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes. *Bioorg. Med. Chem.* **1993**, *1*, 415–422. [CrossRef]

61. Narayanan, A.; Kehn-Hall, K.; Senina, S.; Lundberg, L.; Van Duyne, R.; Guendel, I.; Das, R.; Baer, A.; Bethel, L.; Turell, M. Curcumin inhibits Rift Valley fever virus replication in human cells. *J. Biol. Chem.* **2012**, *287*, 33198–33214. [CrossRef]
62. Ali, A.; Banerjea, A.C. Curcumin inhibits HIV-1 by promoting Tat protein degradation. *Sci. Rep.* **2016**, *6*, 27539. [CrossRef]
63. Jafari, M.; Ghadami, E.; Dadkhah, T.; Akhavan-Niaki, H. PI3k/AKT signaling pathway: Erythropoiesis and beyond. *J. Cell. Physiol.* **2019**, *234*, 2373–2385. [CrossRef]
64. Diehl, N.; Schaal, H. Make yourself at home: Viral hijacking of the PI3K/Akt signaling pathway. *Viruses* **2013**, *5*, 3192–3212. [CrossRef]
65. Shi, Q.; Hoffman, B.; Liu, Q. PI3K-Akt signaling pathway upregulates hepatitis C virus RNA translation through the activation of SREBPs. *Virology* **2016**, *490*, 99–108. [CrossRef]
66. Lee, P.J.; Alam, J.; Wiegand, G.W.; Choi, A. Overexpression of heme oxygenase-1 in human pulmonary epithelial cells results in cell growth arrest and increased resistance to hyperoxia. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 10393–10398. [CrossRef] [PubMed]
67. Hamilton, S.K.; Ikizler, M.R.; Wallen, C.; Wright, P.F.; Harth, E. Effective delivery of IgG-antibodies into infected cells via dendritic molecular transporter conjugate IgGMT. *Mol. Biosyst.* **2008**, *4*, 1209–1211. [CrossRef] [PubMed]
68. Mettenleiter, T.C.; Sobrino, F. *Animal Viruses: Molecular Biology*; Caister Academic Press: Norfolk, VA, USA, 2008; Volume 1.
69. Richart, S.M.; Li, Y.-L.; Mizushina, Y.; Chang, Y.-Y.; Chung, T.-Y.; Chen, G.-H.; Tzen, J.T.-C.; Shia, K.-S.; Hsu, W.-L. Synergic effect of curcumin and its structural analogue (Monoacetylcurcumin) on anti-influenza virus infection. *J. Food Drug Anal.* **2018**, *26*, 1015–1023. [CrossRef] [PubMed]
70. Yang, X.X.; Li, C.M.; Huang, C.Z. Curcumin modified silver nanoparticles for highly efficient inhibition of respiratory syncytial virus infection. *Nanoscale* **2016**, *8*, 3040–3048. [CrossRef]
71. Phansalkar, P.S.; Zhang, Z.; Verenich, S.; Gerk, P.M. Pharmacokinetics and bioavailability enhancement of natural products. In *Natural Products for Cancer Chemoprevention*; Springer: Berlin/Heidelberg, Germany, 2020; pp. 109–141.
72. Bawa, G.; Khurana, N.; Singh, A. Clinical Uses of Piperine: A Review. *World J. Pharm. Res.* **2021**, *10*, 2232–2270.
73. Lin, C.J.; Chang, L.; Chu, H.W.; Lin, H.J.; Chang, P.C.; Wang, R.Y.; Unnikrishnan, B.; Mao, J.Y.; Chen, S.Y.; Huang, C.C. High amplification of the antiviral activity of curcumin through transformation into carbon quantum dots. *Small* **2019**, *15*, 1902641. [CrossRef]
74. Loutfy, S.A.; Elberry, M.H.; Farroh, K.Y.; Mohamed, H.T.; Mohamed, A.A.; Mohamed, E.B.; Faraag, A.H.I.; Mousa, S.A. Antiviral activity of chitosan nanoparticles encapsulating curcumin against hepatitis C virus genotype 4a in human hepatoma cell lines. *Int. J. Nanomed.* **2020**, *15*, 2699. [CrossRef]
75. Kharisma, V.D.; Agatha, A.; Ansori, A.N.M.; Widyananda, M.H.; Rizky, W.C.; Dings, T.G.A.; Marina Derkho8, I.L.; Antonius, Y.; Rosadi, I.; Zainul, R. Herbal combination from *Moringa oleifera* Lam. and *Curcuma longa* L. as SARS-CoV-2 antiviral via dual inhibitor pathway: A viroinformatics approach. *J. Pharm. Pharmacogn. Res.* **2021**, *10*, 138–146. [CrossRef]
76. Nabila, N.; Suada, N.K.; Denis, D.; Yohan, B.; Adi, A.C.; Veterini, A.S.; Anindya, A.L.; Sasmono, R.T.; Rachmawati, H. Antiviral action of curcumin encapsulated in nanoemulsion against four serotypes of dengue virus. *Pharm. Nanotechnol.* **2020**, *8*, 54–62. [CrossRef]
77. Singh, R.K.; Rai, D.; Yadav, D.; Bhargava, A.; Balzarini, J.; De Clercq, E. Synthesis, antibacterial and antiviral properties of curcumin bioconjugates bearing dipeptide, fatty acids and folic acid. *Eur. J. Med. Chem.* **2010**, *45*, 1078–1086. [CrossRef]
78. Ting, D.; Dong, N.; Fang, L.; Lu, J.; Bi, J.; Xiao, S.; Han, H. Multisite inhibitors for enteric coronavirus: Antiviral cationic carbon dots based on curcumin. *ACS Appl. Nano Mater.* **2018**, *1*, 5451–5459. [CrossRef]
79. Zandi, K.; Ramedani, E.; Mohammadi, K.; Tajbakhsh, S.; Deilami, I.; Rastian, Z.; Fouladvand, M.; Yousefi, F.; Farshadpour, F. Evaluation of antiviral activities of curcumin derivatives against HSV-1 in Vero cell line. *Nat. Prod. Commun.* **2010**, *5*, 1935–1938. [CrossRef] [PubMed]
80. Kutluay, S.B.; Doroghazi, J.; Roemer, M.E.; Triezenberg, S. Curcumin inhibits herpes simplex virus immediate-early gene expression by a mechanism independent of p300/CBP histone acetyltransferase activity. *Virology* **2008**, *373*, 239–247. [CrossRef] [PubMed]
81. Bonfim, C.M.d.; Monteleoni, L.F.; Calmon, M.d.F.; Cândido, N.M.; Provazzi, P.J.S.; Lino, V.d.S.; Rabachini, T.; Sichero, L.; Villa, L.L.; Quintana, S.M. Antiviral activity of curcumin-nanoemulsion associated with photodynamic therapy in vulvar cell lines transducing different variants of HPV-16. *Artif. Cells Nanomed. Biotechnol.* **2020**, *48*, 515–524. [CrossRef]
82. Ma, Y.; Frutos-Beltrán, E.; Kang, D.; Pannecouque, C.; De Clercq, E.; Menéndez-Arias, L.; Liu, X.; Zhan, P. Medicinal chemistry strategies for discovering antivirals effective against drug-resistant viruses. *Chem. Soc. Rev.* **2021**, *50*, 4514–4540. [CrossRef]
83. Xiong, R.; Zhang, L.; Li, S.; Sun, Y.; Ding, M.; Wang, Y.; Zhao, Y.; Wu, Y.; Shang, W.; Jiang, X.J.P.; et al. Novel and potent inhibitors targeting DHODH are broad-spectrum antivirals against RNA viruses including newly-emerged coronavirus SARS-CoV-2. *Protein Cell* **2020**, *11*, 723–739. [CrossRef]
84. Choi, Y.-M.; Lee, S.-Y.; Kim, B.-J. Naturally occurring hepatitis B virus reverse transcriptase mutations related to potential antiviral drug resistance and liver disease progression. *World J. Gastroenterol.* **2018**, *24*, 1708. [CrossRef]
85. Rhee, S.-Y.; Taylor, J.; Wadhera, G.; Ben-Hur, A.; Brutlag, D.L.; Shafer, R.W. Genotypic predictors of human immunodeficiency virus type 1 drug resistance. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 17355–17360. [CrossRef]
86. Shome, S.; Talukdar, A.D.; Choudhury, M.D.; Bhattacharya, M.K.; Upadhyaya, H. Curcumin as potential therapeutic natural product: A nanobiotechnological perspective. *J. Pharm. Pharmacol.* **2016**, *68*, 1481–1500. [CrossRef]

87. Talodthaisong, C.; Plaeyao, K.; Mongseetong, C.; Boonta, W.; Srichaiyapol, O.; Patramanon, R.; Kayunkid, N.; Kulchat, S.J.N. The Decoration of ZnO Nanoparticles by Gamma Aminobutyric Acid, Curcumin Derivative and Silver Nanoparticles: Synthesis, Characterization and Antibacterial Evaluation. *Nanomaterials* **2021**, *11*, 442. [CrossRef]
88. Basniwal, R.K.; Buttar, H.S.; Jain, V.K.; Jain, N. Curcumin nanoparticles: Preparation, characterization, and antimicrobial study. *J. Agric. Food Chem.* **2011**, *59*, 2056–2061. [CrossRef]
89. Tomita, M.; Kawakami, H.; Uchihara, J.-n.; Okudaira, T.; Masuda, M.; Takasu, N.; Matsuda, T.; Ohta, T.; Tanaka, Y.; Mori, N. RETRACTED: Curcumin suppresses constitutive activation of AP-1 by downregulation of JunD protein in HTLV-1-infected T-cell lines. *Leuk. Res.* **2006**, *30*, 313–321. [CrossRef] [PubMed]
90. Divya, C.S.; Pillai, M.R. Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis. *Mol. Carcinog. Publ. Coop. Univ. Tex. MD Anderson Cancer Cent.* **2006**, *45*, 320–332. [CrossRef] [PubMed]
91. Prusty, B.K.; Das, B.C. Constitutive activation of transcription factor AP-1 in cervical cancer and suppression of human papillomavirus (HPV) transcription and AP-1 activity in HeLa cells by curcumin. *Int. J. Cancer* **2005**, *113*, 951–960. [CrossRef]
92. Dutta, K.; Ghosh, D.; Basu, A. Curcumin protects neuronal cells from Japanese encephalitis virus-mediated cell death and also inhibits infective viral particle formation by dysregulation of ubiquitin–proteasome system. *J. Neuroimmune Pharmacol.* **2009**, *4*, 328–337. [CrossRef]
93. Si, X.; Wang, Y.; Wong, J.; Zhang, J.; McManus, B.M.; Luo, H. Dysregulation of the ubiquitin-proteasome system by curcumin suppresses coxsackievirus B3 replication. *J. Virol.* **2007**, *81*, 3142–3150. [CrossRef]
94. Kim, K.; Kim, K.H.; Kim, H.Y.; Cho, H.K.; Sakamoto, N.; Cheong, J. Curcumin inhibits hepatitis C virus replication via suppressing the Akt-SREBP-1 pathway. *FEBS Lett.* **2010**, *584*, 707–712. [CrossRef]
95. Bourne, K.Z.; Bourne, N.; Reising, S.F.; Stanberry, L.R. Plant products as topical microbicide candidates: Assessment of in vitro and in vivo activity against herpes simplex virus type 2. *Antivir. Res.* **1999**, *42*, 219–226. [CrossRef]
96. Chen, D.-Y.; Shien, J.-H.; Tiley, L.; Chiou, S.-S.; Wang, S.-Y.; Chang, T.-J.; Lee, Y.-J.; Chan, K.-W.; Hsu, W.-L. Curcumin inhibits influenza virus infection and haemagglutination activity. *Food Chem.* **2010**, *119*, 1346–1351. [CrossRef]
97. Li, C.J.; Zhang, L.J.; Dezube, B.J.; Crumpacker, C.S.; Pardee, A.B. Three inhibitors of type 1 human immunodeficiency virus long terminal repeat-directed gene expression and virus replication. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 1839–1842. [CrossRef]
98. Mazumder, A.; Raghavan, K.; Weinstein, J.; Kohn, K.W.; Pommier, Y. Inhibition of human immunodeficiency virus type-1 integrase by curcumin. *Biochem. Pharmacol.* **1995**, *49*, 1165–1170. [CrossRef]
99. Balasubramanyam, K.; Varier, R.A.; Altaf, M.; Swaminathan, V.; Siddappa, N.B.; Ranga, U.; Kundu, T.K. Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. *J. Biol. Chem.* **2004**, *279*, 51163–51171. [CrossRef] [PubMed]
100. Lv, Y.; An, Z.; Chen, H.; Wang, Z.; Liu, L. Mechanism of curcumin resistance to human cytomegalovirus in HELF cells. *BMC Complement. Altern. Med.* **2014**, *14*, 284. [CrossRef]
101. Ferreira, V.H.; Nazli, A.; Dizzell, S.E.; Mueller, K.; Kaushic, C. The anti-inflammatory activity of curcumin protects the genital mucosal epithelial barrier from disruption and blocks replication of HIV-1 and HSV-2. *PLoS ONE* **2015**, *10*, e0124903. [CrossRef] [PubMed]
102. Zhu, L.; Ding, X.; Zhang, D.; Ch, Y.; Wang, J.; Ndegwa, E.; Zhu, G. Curcumin inhibits bovine herpesvirus type 1 entry into MDBK cells. *Acta Virol.* **2015**, *59*, 221–227. [CrossRef] [PubMed]
103. Obata, K.; Kojima, T.; Masaki, T.; Okabayashi, T.; Yokota, S.; Hirakawa, S.; Nomura, K.; Takasawa, A.; Murata, M.; Tanaka, S. Curcumin prevents replication of respiratory syncytial virus and the epithelial responses to it in human nasal epithelial cells. *PLoS ONE* **2013**, *8*, e70225. [CrossRef]
104. Manoharan, Y.; Haridas, V.; Vasanthakumar, K.C.; Muthu, S.; Thavoorullah, F.F.; Shetty, P. Curcumin: A Wonder Drug as a Preventive Measure for COVID-19 Management. *Indian J. Clin. Biochem.* **2020**, *35*, 373–375. [CrossRef]
105. D'Souza, S.P.; Chavannavar, S.V.; Kanchanashri, B.; Niveditha, S.B. Pharmaceutical perspectives of spices and condiments as alternative antimicrobial remedy. *J. Evid.-Based Integr. Med.* **2017**, *22*, 1002–1010. [CrossRef]
106. Khan, R.U.; Naz, S.; Javdani, M.; Nikousefat, Z.; Selvaggi, M.; Tufarelli, V.; Laudadio, V. The use of turmeric (*Curcuma longa*) in poultry feed. *World's Poult. Sci. J.* **2012**, *68*, 97–103. [CrossRef]
107. Rao, R.V.; Descamps, O.; John, V.; Bredesen, D.E. Ayurvedic medicinal plants for Alzheimer's disease: A review. *Alzheimer's Res. Ther.* **2012**, *4*, 22. [CrossRef]
108. Pan, S.-Y.; Zhou, S.-F.; Gao, S.-H.; Yu, Z.-L.; Zhang, S.-F.; Tang, M.-K.; Sun, J.-N.; Ma, D.-L.; Han, Y.-F.; Fong, W.-F.; et al. New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. *Evid.-Based Complement. Altern. Med.* **2013**, *2013*, 627375. [CrossRef] [PubMed]
109. Malgaonkar, M.; Shirolkar, A.; Murthy, S.N.; Pawar, S. Ayurvedic Plants with Antidiabetic Potential. In *Medicinal Plants-Recent Advances in Research and Development*; Springer: Berlin/Heidelberg, Germany, 2016; pp. 439–468.
110. Krup, V.; Prakash, L.H.; Harini, A. Pharmacological activities of turmeric (*Curcuma longa* Linn): A review. *J. Homeopath. Ayurvedic Med.* **2013**, *2*, 1000133. [CrossRef]
111. Shahrajabian, M.H.; Sun, W.; Cheng, Q. Clinical aspects and health benefits of ginger (*Zingiber officinale*) in both traditional Chinese medicine and modern industry. *Acta Agric. Scand. Sect. B—Soil Plant Sci.* **2019**, *69*, 546–556. [CrossRef]

112. Rajkumari, S.; Sanatombi, K. Nutritional value, phytochemical composition, and biological activities of edible Curcuma species: A review. *Int. J. Food Prop.* **2017**, *20*, S2668–S2687. [CrossRef]
113. Gilani, S.J.; Imam, S.S.; Jafar, M.; Alshehri, S.; Taleuzzaman, M.; Jahangir, M.A. Curcumin Nanomedicine and Their Application in the Management of Disease. In *Biomarkers as Targeted Herbal Drug Discovery*; Apple Academic Press: Palm Bay, FL, USA, 2021; pp. 43–63.
114. Khezri, K.; Saeedi, M.; Mohammadamini, H.; Zakaryaei, A.S. A comprehensive review of the therapeutic potential of curcumin nanoformulations. *Phytother. Res.* **2021**, *35*, 5527–5563. [CrossRef] [PubMed]
115. Lv, H.; Wang, Y.; Yang, X.; Ling, G.; Zhang, P. Application of curcumin nanoformulations in Alzheimer's disease: Prevention, diagnosis and treatment. *Nutr. Neurosci.* **2022**, 1–16. [CrossRef]
116. Quispe, C.; Herrera-Bravo, J.; Javed, Z.; Khan, K.; Raza, S.; Gulsunoglu-Konuskan, Z.; Daştan, S.D.; Sytar, O.; Martorell, M.; Sharifi-Rad, J.; et al. Therapeutic applications of curcumin in diabetes: A review and perspective. *BioMed Res. Int.* **2022**, *2022*, 1–14. [CrossRef]
117. Kabir, M.T.; Rahman, M.H.; Akter, R.; Behl, T.; Kaushik, D.; Mittal, V.; Pandey, P.; Akhtar, M.F.; Saleem, A.; Albadrani, G.M.; et al. Potential Role of Curcumin and Its Nanoformulations to Treat Various Types of Cancers. *Biomolecules* **2021**, *11*, 392. [CrossRef]
118. Maleki Dizaj, S.; Alipour, M.; Dalir Abdolahinia, E.; Ahmadian, E.; Eftekhari, A.; Forouhandeh, H.; Rahbar Saadat, Y.; Sharifi, S.; Zununi Vahed, S. Curcumin nanoformulations: Beneficial nanomedicine against cancer. *Phytother. Res.* **2022**, *36*, 1156–1181. [CrossRef]
119. Haghnegahdar, N.; Abbasi Tarighat, M.; Dastan, D. Curcumin-functionalized nanocomposite AgNPs/SDS/MWCNTs for electrocatalytic simultaneous determination of dopamine, uric acid, and guanine in co-existence of ascorbic acid by glassy carbon electrode. *J. Mater. Sci. Mater. Electron.* **2021**, *32*, 5602–5613. [CrossRef]
120. Peng, Y.; Chen, L.; Ye, S.; Kang, Y.; Liu, J.; Zeng, S.; Yu, L. Research and development of drug delivery systems based on drug transporter and nano-formulation. *Asian J. Pharm. Sci.* **2020**, *15*, 220–236. [CrossRef]
121. Walker, D.A.; Kowalczyk, B.; de la Cruz, M.O.; Grzybowski, B.A. Electrostatics at the nanoscale. *Nanoscale* **2011**, *3*, 1316–1344. [CrossRef] [PubMed]
122. Halevas, E.; Mavroidi, B.; Swanson, C.H.; Smith, G.C.; Moschona, A.; Hadjispyrou, S.; Salifoglou, A.; Pantazaki, A.A.; Pelecanou, M.; Litsardakis, G. Magnetic cationic liposomal nanocarriers for the efficient drug delivery of a curcumin-based vanadium complex with anticancer potential. *J. Inorg. Biochem.* **2019**, *199*, 110778. [CrossRef] [PubMed]
123. Chen, K.; Xu, Y.; Rana, S.; Miranda, O.R.; Dubin, P.L.; Rotello, V.M.; Sun, L.; Guo, X. Electrostatic selectivity in protein-nanoparticle interactions. *Biomacromolecules* **2011**, *12*, 2552–2561. [CrossRef] [PubMed]
124. Hosseini, S.M.H.; Emam-Djomeh, Z.; Sabatino, P.; Van der Meeren, P. Nanocomplexes arising from protein-polysaccharide electrostatic interaction as a promising carrier for nutraceutical compounds. *Food Hydrocoll.* **2015**, *50*, 16–26. [CrossRef]
125. Appel, E.A.; Tibbitt, M.W.; Greer, J.M.; Fenton, O.S.; Kreuels, K.; Anderson, D.G.; Langer, R. Exploiting Electrostatic Interactions in Polymer-Nanoparticle Hydrogels. *ACS Macro Lett.* **2015**, *4*, 848–852. [CrossRef]
126. Sims, K.R., Jr.; He, B.; Koo, H.; Benoit, D.S.W. Electrostatic Interactions Enable Nanoparticle Delivery of the Flavonoid Myricetin. *ACS Omega* **2020**, *5*, 12649–12659. [CrossRef]
127. Chen, S.; McClements, D.J.; Jian, L.; Han, Y.; Dai, L.; Mao, L.; Gao, Y. Core-Shell Biopolymer Nanoparticles for Co-Delivery of Curcumin and Piperine: Sequential Electrostatic Deposition of Hyaluronic Acid and Chitosan Shells on the Zein Core. *ACS Appl. Mater. Interfaces* **2019**, *11*, 38103–38115. [CrossRef]
128. Papagiannopoulos, A.; Sklapani, A. Xanthan-based polysaccharide/protein nanoparticles: Preparation, characterization, encapsulation and stabilization of curcumin. *Carbohydr. Polym. Technol. Appl.* **2021**, *2*, 100075. [CrossRef]
129. Li, H.; Zhang, X.; Zhao, C.; Zhang, H.; Chi, Y.; Wang, L.; Zhang, H.; Bai, S.; Zhang, X. Entrapment of curcumin in soy protein isolate using the pH-driven method: Nanoencapsulation and formation mechanism. *LWT* **2022**, *153*, 112480. [CrossRef]
130. Vatanparast, H.; Shahabi, F.; Bahramian, A.; Javadi, A.; Miller, R. The Role of Electrostatic Repulsion on Increasing Surface Activity of Anionic Surfactants in the Presence of Hydrophilic Silica Nanoparticles. *Sci. Rep.* **2018**, *8*, 7251. [CrossRef]
131. Bian, T.; Gardin, A.; Gemen, J.; Houben, L.; Perego, C.; Lee, B.; Elad, N.; Chu, Z.; Pavan, G.M.; Klajn, R. Electrostatic co-assembly of nanoparticles with oppositely charged small molecules into static and dynamic superstructures. *Nat. Chem.* **2021**, *13*, 940–949. [CrossRef] [PubMed]
132. Karatas, D.; Tekin, A.; Bahadori, F.; Celik, M.S. Interaction of curcumin in a drug delivery system including a composite with poly(lactic-co-glycolic acid) and montmorillonite: A density functional theory and molecular dynamics study. *J. Mater. Chem. B* **2017**, *5*, 8070–8082. [CrossRef] [PubMed]
133. Zahedipour, F.; Hosseini, S.A.; Sathyapalan, T.; Majeed, M.; Jamialahmadi, T.; Al-Rasadi, K.; Banach, M.; Sahebkar, A. Potential effects of curcumin in the treatment of COVID-19 infection. *Phytother. Res.* **2020**, *34*, 2911–2920. [CrossRef]
134. Astuti, I.; Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. *Diabetes Metab. Syndr.* **2020**, *14*, 407–412. [CrossRef]
135. Celik, C.; Gencay, A.; Ocsoy, I. Can food and food supplements be deployed in the fight against the COVID-19 pandemic? *Biochim. Biophys. Acta Gen. Subj.* **2021**, *1865*, 129801. [CrossRef] [PubMed]
136. Kow, C.S.; Ramachandram, D.S.; Hasan, S.S. The effect of curcumin on the risk of mortality in patients with COVID-19: A systematic review and meta-analysis of randomized trials. *Phytother. Res.* **2022**. [CrossRef]

137. Vahedian-Azimi, A.; Abbasifard, M.; Rahimi-Bashar, F.; Guest, P.C.; Majeed, M.; Mohammadi, A.; Banach, M.; Jamialahmadi, T.; Sahebkar, A. Effectiveness of Curcumin on Outcomes of Hospitalized COVID-19 Patients: A Systematic Review of Clinical Trials. *Nutrients* **2022**, *14*, 256. [CrossRef]
138. Zhou, Y.W.; Xie, Y.; Tang, L.S.; Pu, D.; Zhu, Y.J.; Liu, J.Y.; Ma, X.L. Therapeutic targets and interventional strategies in COVID-19: Mechanisms and clinical studies. *Signal Transduct. Target. Ther.* **2021**, *6*, 317. [CrossRef]
139. Krumm, Z.A.; Lloyd, G.M.; Francis, C.P.; Nasif, L.H.; Mitchell, D.A.; Golde, T.E.; Giasson, B.I.; Xia, Y. Precision therapeutic targets for COVID-19. *Virol. J.* **2021**, *18*, 66. [CrossRef]
140. Matthews, D.A.; Dragovich, P.S.; Webber, S.E.; Fuhrman, S.A.; Patick, A.K.; Zalman, L.S.; Hendrickson, T.F.; Love, R.A.; Prins, T.J.; Marakovits, J.T.; et al. Structure-assisted design of mechanism-based irreversible inhibitors of human rhinovirus 3C protease with potent antiviral activity against multiple rhinovirus serotypes. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 11000–11007. [CrossRef]
141. Bruningk, S.C.; Klatt, J.; Stange, M.; Mari, A.; Brunner, M.; Roloff, T.-C.; Seth-Smith, H.; Schweitzer, M.; Leuzinger, K.; Sogaard, K.K. Determinants of SARS-CoV-2 transmission to guide vaccination strategy in an urban area. *Virus Evol.* **2022**, *8*, veac002. [CrossRef] [PubMed]
142. Dhar, S.; Bhattacharjee, P. Promising role of curcumin against viral diseases emphasizing COVID-19 management: A review on the mechanistic insights with reference to host-pathogen interaction and immunomodulation. *J. Funct. Foods* **2021**, *82*, 104503. [CrossRef] [PubMed]
143. Dourado, D.; Freire, D.T.; Pereira, D.T.; Amaral-Machado, L.; Alencar, N.; de Barros, A.L.B.; Egito, E.S.T. Will curcumin nanosystems be the next promising antiviral alternatives in COVID-19 treatment trials? *Biomed. Pharmacother.* **2021**, *139*, 111578. [CrossRef] [PubMed]
144. Fu, Y.S.; Chen, T.H.; Weng, L.; Huang, L.; Lai, D.; Weng, C.F. Pharmacological properties and underlying mechanisms of curcumin and prospects in medicinal potential. *Biomed. Pharmacother.* **2021**, *141*, 111888. [CrossRef]
145. Widjaja, S.S.; Rusdiana, R.; Amelia, R. Curcumin: Boosting the immunity of COVID-19-vaccinated populations. *J. Adv. Pharm. Technol. Res.* **2020**, *13*, 187. [CrossRef]
146. Suresh, P.S. Curcumin and Coagulopathy in the COVID-19 Era. *Indian J. Clin. Biochem.* **2020**, *35*, 504–505. [CrossRef]
147. Hassaniazad, M.; Eftekhar, E.; Inchehsablagh, B.R.; Kamali, H.; Tousi, A.; Jaafari, M.R.; Rafat, M.; Fathalipour, M.; Nikoofal-Sahlabadi, S.; Gouklani, H.; et al. A triple-blind, placebo-controlled, randomized clinical trial to evaluate the effect of curcumin-containing nanomicelles on cellular immune responses subtypes and clinical outcome in COVID-19 patients. *Phytother. Res.* **2021**, *35*, 6417–6427. [CrossRef]
148. Pawar, K.S.; Mastud, R.N.; Pawar, S.K.; Pawar, S.S.; Bhoite, R.R.; Bhoite, R.R.; Kulkarni, M.V.; Deshpande, A.R. Oral Curcumin with Piperine as Adjuvant Therapy for the Treatment of COVID-19: A Randomized Clinical Trial. *Front. Pharmacol.* **2021**, *12*, 669362. [CrossRef]
149. Pourhajibagher, M.; Azimi, M.; Haddadi-Asl, V.; Ahmadi, H.; Gholamzad, M.; Ghorbanpour, S.; Bahador, A. Robust antimicrobial photodynamic therapy with curcumin-poly (lactic-co-glycolic acid) nanoparticles against COVID-19: A preliminary in vitro study in Vero cell line as a model. *Photodiagnosis Photodyn. Ther.* **2021**, *34*, 102286. [CrossRef]
150. Rattis, B.A.C.; Ramos, S.G.; Celes, M.R.N. Curcumin as a Potential Treatment for COVID-19. *Front. Pharmacol.* **2021**, *12*, 675287. [CrossRef]
151. Bormann, M.; Alt, M.; Schipper, L.; van de Sand, L.; Le-Trilling, V.T.K.; Rink, L.; Heinen, N.; Madel, R.J.; Otte, M.; Wuensch, K.; et al. Turmeric Root and Its Bioactive Ingredient Curcumin Effectively Neutralize SARS-CoV-2 In Vitro. *Viruses* **2021**, *13*, 1914. [CrossRef] [PubMed]
152. Askari, G.; Sahebkar, A.; Soleimani, D.; Mahdavi, A.; Rafiee, S.; Majeed, M.; Khorvash, F.; Iraj, B.; Elyasi, M.; Rouhani, M.H. The efficacy of curcumin-piperine co-supplementation on clinical symptoms, duration, severity, and inflammatory factors in COVID-19 outpatients: A randomized double-blind, placebo-controlled trial. *Trials* **2022**, *23*, 472. [CrossRef] [PubMed]
153. Askari, G.; Alikiaii, B.; Soleimani, D.; Sahebkar, A.; Mirjalili, M.; Feizi, A.; Iraj, B.; Bagherniya, M.J.T. Effect of curcumin-pipeine supplementation on clinical status, mortality rate, oxidative stress, and inflammatory markers in critically ill ICU patients with COVID-19: A structured summary of a study protocol for a randomized controlled trial. *Trials* **2021**, *22*, 434. [CrossRef]
154. Schraufstätter, E.; Bernt, H. Antibacterial action of curcumin and related compounds. *Nature* **1949**, *164*, 456–457. [CrossRef] [PubMed]
155. Strimpakos, A.S.; Sharma, R.A. Curcumin: Preventive and therapeutic properties in laboratory studies and clinical trials. Antioxid. *Redox Signal.* **2008**, *10*, 511–546. [CrossRef]
156. Aggarwal, B.B.; Gupta, S.C.; Sung, B. Curcumin: An orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. *Br. J. Pharmacol.* **2013**, *169*, 1672–1692. [CrossRef]
157. Chainani-Wu, N. Safety and anti-inflammatory activity of curcumin: A component of tumeric (*Curcuma longa*). *J. Altern. Complement. Med.* **2003**, *9*, 161–168. [CrossRef]
158. Prasad, S.; Tyagi, A.K.; Aggarwal, B.B. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: The golden pigment from golden spice. *Cancer Res. Treat. Off. J. Korean Cancer Assoc.* **2014**, *46*, 2–18. [CrossRef]
159. Alafiatayo, A.A.; Lai, K.-S.; Syahida, A.; Mahmood, M.; Shaharuddin, N.A.; Medicine, A. Phytochemical evaluation, embryotoxicity, and teratogenic effects of *Curcuma longa* extract on zebrafish (*Danio rerio*). *Evid.-Based Complement. Altern. Med.* **2019**, *2019*, 3807207. [CrossRef]

160. Hsu, C.-H.; Cheng, A.-L. Clinical studies with curcumin. In *The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease*; Springer Science+Business Media: Berlin/Heidelberg, Germany, 2007; pp. 471–480.
161. Kuptniratsaikul, V.; Thanakhumtorn, S.; Chinswangwatanakul, P.; Wattanamongkonsil, L.; Thamlikitkul, V. Efficacy and safety of Curcuma domestica extracts in patients with knee osteoarthritis. *J. Altern. Complement. Med.* **2009**, *15*, 891–897. [CrossRef]
162. Salehi, B.; Stojanović-Radić, Z.; Matejić, J.; Sharifi-Rad, M.; Kumar, N.V.A.; Martins, N.; Sharifi-Rad, J. The therapeutic potential of curcumin: A review of clinical trials. *Eur. J. Med. Chem.* **2019**, *163*, 527–545. [CrossRef] [PubMed]
163. Yamauchi, Y.; Izumi, Y.; Asakura, K.; Hayashi, Y.; Nomori, H. Curcumin induces autophagy in ACC-MESO-1 Cells. *Phytother. Res.* **2012**, *26*, 1779–1783. [CrossRef] [PubMed]
164. Purohit, R.N.; Bhatt, M.; Purohit, K.; Acharya, J.; Kumar, R.; Garg, R.J. Clinical and radiological evaluation of turmeric powder as a pulpotomy medicament in primary teeth: An in vivo study. *Int. J. Clin. Pediatr. Dent.* **2017**, *10*, 37.
165. Ullah, F.; Liang, A.; Rangel, A.; Gyengesi, E.; Niedermayer, G.; Münch, G. High bioavailability curcumin: An anti-inflammatory and neurosupportive bioactive nutrient for neurodegenerative diseases characterized by chronic neuroinflammation. *Arch. Toxicol.* **2017**, *91*, 1623–1634. [CrossRef] [PubMed]
166. AloK, A.; Singh, I.D.; Singh, S.; Kishore, M.; Jha, P.C. Curcumin–pharmacological actions and its role in oral submucous fibrosis: A review. *J. Clin. Diagn. Res.* **2015**, *9*, ZE01. [CrossRef]
167. Booker, A.; Chatzinasiou, L.; Heinrich, M.; MacLennan, E.; Mackonochie, M. Turmeric (*Curcuma longa* L.) products: What quality differences exist? *J. Herb. Med.* **2019**, *17*, 100281.
168. Choi, Y.-H.; Yan, G.-H.; Chai, O.H.; Song, C.H. Inhibitory effects of curcumin on passive cutaneous anaphylactoid response and compound 48/80-induced mast cell activation. *Anat. Cell Biol.* **2010**, *43*, 36–43. [CrossRef]
169. Xu, D.; Tian, W.; Shen, H. Curcumin prevents induced drug resistance: A novel function? *Chin. J. Cancer Res.* **2011**, *23*, 218–223. [CrossRef]
170. Bhatt, N.A.; Singh, A.; Sharma, R. Pharmacological Activities of *Curcuma Longa*: A Review. *Eur. J. Mol. Clin. Med.* **2021**, *8*, 2021.
171. Dohare, P.; Garg, P.; Jagannathan, N.; Ray, M. Neuroprotective efficacy and therapeutic window of curcuma oil: In rat embolic stroke model. *BMC Complementary Altern. Med.* **2008**, *8*, 55. [CrossRef]
172. Dhiman, A.K. *Common Drug Plants and Ayurvedic Remedies*; Reference Press: New Delhi, India, 2004.
173. Oluwafemi, R.; Olawale, I.; Alagbe, J.; Sciences, V. Recent trends in the utilization of medicinal plants as growth promoters in poultry nutrition—A review. *Res. Agric. Vet. Sci.* **2020**, *4*, 5–11.
174. Park, J.; Conteas, C.N. Anti-carcinogenic properties of curcumin on colorectal cancer. *World J. Gastrointest. Oncol.* **2010**, *2*, 169. [CrossRef] [PubMed]
175. Parasramka, M.A.; Gupta, S.V. Synergistic effect of garcinol and curcumin on antiproliferative and apoptotic activity in pancreatic cancer cells. *J. Oncol.* **2012**, *2012*, 709739. [CrossRef] [PubMed]