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Review On: Curcumin As An Antiviral Agent

Ms. Aliya Ebrahim Pinjari[1], Mrs. Mangal S. Gaikwad[2], Mr. Ajinkya Anna Kavitake[3], Ms. Aishwarya Deshmukh[4], Shaikh Md Jaid Zafar Aabid[5]

[1,3,4,5]Student, Delight College of Pharmacy, Koregaon Bhima, Pune. Maharashtra, India

[2]Associate professor Pharmacognosy Delight College of Pharmacy, Koregaon Bhima, Pune, Maharashtra, India.

Abstract

Here is a thorough synopsis of curcumin's function as an antiviral agent for this review. Turmeric's primary component, curcumin, has anti-inflammatory, antiviral, antioxidant, anticancer, and antifungal properties and is used as a food additive and medicinal agent. The pharmacological and biological characteristics of curcumin are diverse. Antiviral action against dengue virus, norovirus, HIV, HSV, HPV, and other viruses is produced by curcumin. Curcumin is recommended because norovirus requires phytochemical activity to be treated. Natural products with anti-infective properties, such as curcumin, are well-known for their use in illness prevention, diagnosis, and treatment. Because natural materials are non-toxic and have no adverse effects, they are employed as treatments in alternative medicine. The main usage of curcumin is it is utilized in alleviating abdominal pain. Curcumin works to prevent disease by altering biological processes. Curcumin is a powerful scavenger of ROS and nitrogen species. Utilizing plant extract makes virus prevention safer and more affordable. Usages of pharmaceuticals include ulcers, diabetes, rheumatoid arthritis, atherosclerosis, and more. In the medical field, more medication combinations including curcumin are being produced. Curcumin's bioavailability is its primary disadvantage. As a result, curcumin is crucial for preserving the antiviral characteristic against viruses; it blocks certain viruses at specific locations via specific processes. Curcumin's bioavailability is altered to make it a more potent antiviral agent.

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

Introduction

One member of the Zingiberaceae family of flowering plants is turmeric (Curcuma longa). Turmeric has been utilized in Asian medicine from the prehistoric era. It is a key component of Ayurveda, Siddha, Traditional Chinese, Unani, and the animistic rites of Austronesian peoples. It was initially employed as a dye and then later for its purported benefits in folk medicine. The plant is a rhizomatous perennial herbaceous that is indigenous to the Indian subcontinent and Southeast Asia. It thrives in temperate climates and needs a substantial amount of annual rainfall. Due to the qualities that curcumin, the primary ingredient in turmeric, imparts, rhizomes are typically used fresh or boiled in water, dried, and then crushed into a deep orange-yellow powder that is

frequently used as a colouring and flavouring agent in many Asian cuisines, especially curries, as well as for dyeing. Turmeric powder tastes like heated, bitter black pepper and has an earthy, mustard-like scent. The diversity of Curcuma species is highest in India and Thailand, with a variety of wild species found in other tropical Asian nations. Only specimens from South India were recognized as Curcuma longa, according to recent research, indicating problems with the taxonomy of the species. The phylogeny, connections, intraspecific and interspecific variation, and even the identity of other species and cultivars found in other regions of the world still need to be determined and validated. Several species that are marketed as turmeric in different parts of the world really fall within several morphologically similar taxa that have local names that overlap. The majority of primary healthcare providers, especially in developing countries, have backgrounds in traditional medicine.

1.1 Global Distribution of Curcuma longa

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, and Jawa are among the regions where Curcuma longa was first introduced. Its native habitat is India.

1.2 Botanical description

can reach a height of two meters. The leaves are up to one meter long, oblong or lanceolate, and have a dark green upper surface and a pale green below surface. The length of the blade and the sheath and petiole are nearly equal. Curcuma longa features an underground rhizome and a sterile, pale yellow and reddish bloom with a green and purplish flowering bract. The tough, segmented epidermis of the plant's rhizome is the main reason it is grown. The rhizome has a maximum length of 2.5–7.0 cm and a maximum diameter of 2.5 cm. The rhizome tastes harsh and has a nice scent. Plants of Curcuma longa is grown in tropical and subtropical climates with temperatures

1.3 Morphology of Curcuma longa

The herbaceous perennial plant known as turmeric can reach a height of one meter. The rhizomes are fragrant, cylindrical, brilliant to orange, and branched. There are two rows of alternating leaves. The three components of a leaf are the petiole, blade, and leaf sheath. The leaf sheaths are used to make a false stem. The length of the petiole can vary from 50 to 115 cm. Simple leaf blades can be as long as 230 cm, although the average length is between 76 and 115 cm. They are oblong to elliptical, 38 to 45 cm wide, and taper towards the tip. The tapering upper ends of the white to green, occasionally reddish-purple, stem bracts are found near the top of the inflorescence. Hermaphrodites have triple, zygomorphic blooms. The three calyx teeth are unequal, and the three sepals are white, joined, and covered in fluffy hairs. A 3-centimeter-long corolla tube is formed by the union of the three vibrant yellow petals. The three triangular corolla lobes are 1.0 to 1.5 cm long and have soft, spiky ends at the top. Despite the average corolla lobe being larger than the two lateral ones, only the inner circle's median stamen is viable. Figure 1 illustrates curcumin's morphology.

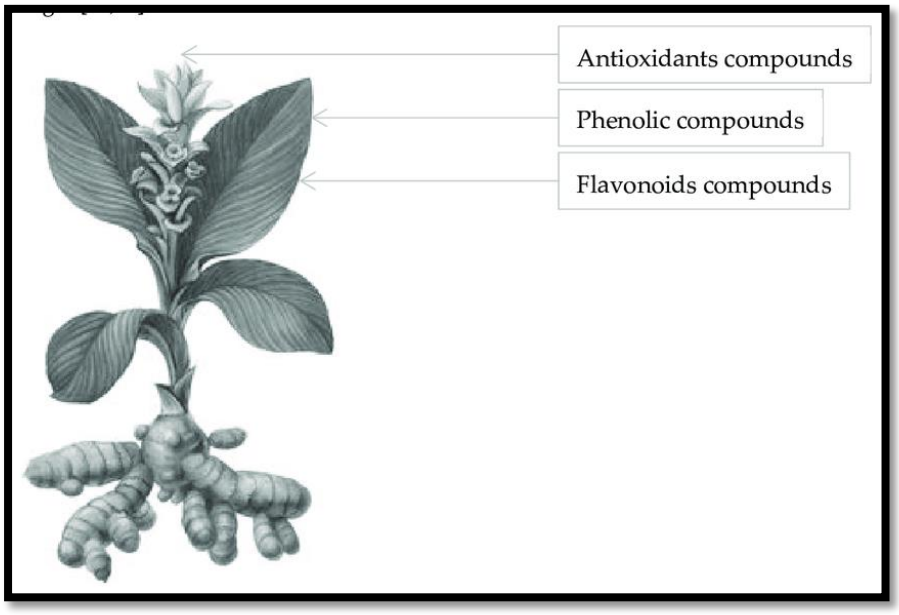

Fig.1 morphology of curcumin

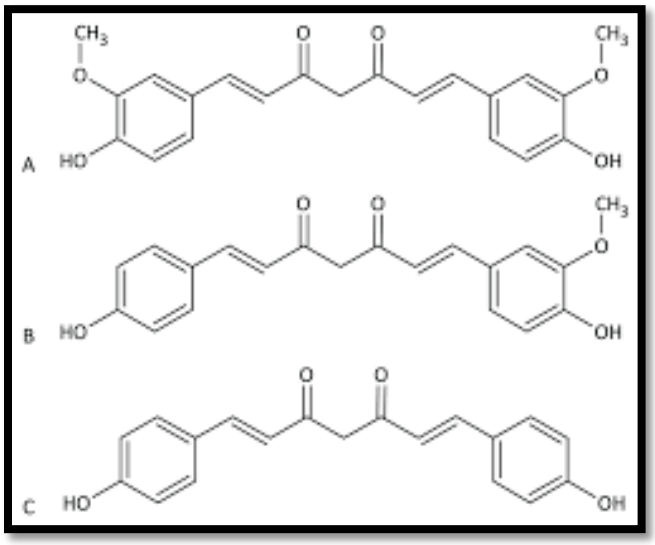

Fig.2 structure of curcumin

1.4 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.

2. RNA viruses

2.1 Human Immunodeficiency Virus

The majority of research on curcumin's anti-viral qualities focuses on how effective it is against HIV. It is true that curcumin can affect HIV function at various stages of the virus' life cycle. Ferreira assessed if curcumin may lessen inflammation in the female genital tract (FGT), which is known to aid in HIV acquisition, given its anti-inflammatory qualities. The primary barrier to HIV entrance is formed mostly by the epithelial cells lining the genital tract (FGT). However, when these cells are exposed to either the complete virus or HIV-1 glycoprotein 120 (gp120), an inflammatory response is triggered, which leads to the downregulation of tight junction (TJ) proteins. Due to this breach in the barrier, HIV-1 might be able to pass through the genital epithelium and infect someone. HIV infection rates may be lowered by pre-treating primary GECs with 5 μM curcumin, which inhibited the down-regulation of TJ proteins. When compared to untreated cells, treatment of chronically infected T-cells (H9 T-cells) with at least 5 μM curcumin significantly reduced the expression of p24, a marker of virus replication, at 24 hpi. If the medium's curcumin was changed every 24 hours, this inhibition could last for several days. Curcumin has the ability to prevent HIV replication by affecting the activity of multiple viral proteins, such as the trans-activator of transcription (Tat) protein, protease, and viral integrase. Curcumin may directly interact with the protein's catalytic center to block the viral integrase. Likewise, curcumin might bind to the HIV-1 protease's active site, according to computer modeling. When it comes to Tat, curcumin administration causes Tat degradation in a time- and dose-dependent manner (20 to 120 μM), which appears to be regulated by a proteasomal route separate from ubiquitination. Additionally, five micrograms of curcumin can prevent the activation of HIV-LTR by inflammatory cytokines caused by infection with other STIs, such as N. gonorrhoeae, HSV-1, and HSV-2. The effectiveness of curcumin-stabilized silver nanoparticles (Cur-AgNP) against HIV has also been studied. Cur-AgNP treatment was shown to be more successful than curcumin alone in reducing HIV-LTR expression in ACH-2 cells.Cur-AgNP did not, however, totally eliminate HIV-1 p24 expression because this protein's levels increased during the infection, albeit at a much slower rate than in cells treated with vehicle. Cur-AgNP also exhibited stronger immunomodulatory effects than curcumin, reducing NF-κB, IL-6, TNF-α, and IL-1β expression. Based on these findings, stabilized nanoparticles may be able to increase curcumin's effectiveness in treating HIV and maybe other viruses.

2.2 Dengue virus

Apart from assessing curcumin's effectiveness against ZIKV, a similar set of chemicals was also examined for their potential to combat dengue virus (DENV). Curcumin demonstrated moderate toxicity (CC50 of 59.42 μM) and reduced plaque formation of all four strains (DENV-1-4; IC50 of 9.37, 3.07, 2.09, and 4.83 μM, respectively) tested in LLC-MK2 cells. An earlier study showed that curcumin likely inhibits DENV-2 indirectly via impacting cellular systems rather than directly on viral functioning, even if the mechanism of inhibition was not addressed. Examined the anti-DENV characteristics of three more synthetic analogy, bisdemethoxycurcumin, and curcumin. Curcumin and its four analogues showed a mild inhibition of viral protease activity (IC50 of around 36–66 μM) in an in vitro activity experiment. Likewise, the DENV2 reporter replicon construct was only marginally inhibited by these compounds, and the acyclic and cyclohexanone curcumin analogues outperformed the natural curcuminoids (50% effective concentration (EC50) of 8.61 and 8.07 μM versus 13.91 μM). In contrast, all analogues of the compounds shown stronger inhibition than curcumin (EC50 of 2.34–6.49 μM versus 13.95 μM, respectively) in a plaque assay, which revealed greater efficacy for the compounds. Curcumin's inhibition of DENV appears to be mediated through impacts on cellular lipid metabolism. Curcumin and its derivatives inhibited the production of lipid droplets (LD) and fatty acid synthase and acetyl-CoA carboxylase, two enzymes that would typically increase DENV infection. Another mechanism that is naturally crucial for DENV entry and

reproduction was caused by curcumin therapy, which likewise resulted in actin filament disarray and polymerization errors.

2.3 Chikungunya virus

HEK 293T cell infection was inhibited by pre-incubating lentiviral vectors pseudo typed with chikungunya virus (CHIKV) envelop proteins E2 and E1 with curcumin (IC50 of 10.79 µM). Time-of-addition experiments using CHIKV encoding a mCherry-tagged viral replicase shown that curcumin therapy reduced the quantity of mCherry positive cells up to two hours post-infection, but had no further effect after that. Curcumin therapy decreased the overall number of cells positive for mCherry, but it had no effect on the pattern or intensity of mCherry staining inside the cells, according to immunofluorescence analysis. Together, these findings imply that curcumin inhibits cell entry and attachment but does not affect virus reproduction, similar to ZIKV. Additionally, curcumin may be changing the structure of glycoproteins on the viral surface.

2.4 Human Respiratory Syncytial Virus

The Human Respiratory Syncytial Virus (HRSV) produced particles of approximately 200 nm when incubated with curcumin-stabilized silver nanoparticles (Cur-AgNP). This particle size is larger than both Cur-AgNP and HRSV particles alone, indicating that Cur-AgNP binds to HRSV directly and that this binding appears to inhibit virus infection. Cur-AgNP pre-treatment was superior to post-infection treatment in terms of lowering virus recovery in cells. A curcumin derivative known as GSCC, which involved loading the drug into β-cyclodextrin and attaching it to sulfonated graphene oxide sheets, was also assessed in comparison to HRSV.
In addition to inhibiting HRSV when administered to cells after infection, this formulation largely suppressed HRSV via blocking viral attachment. The scientists propose that the GSCC sheets function as a competitive inhibitor to sequester viruses away from the cell, hence preventing infection, given the presence of sulfonic acid in the formulation and the fact that HRSV can utilise heparin sulfate for entry. Moreover, the GSCC sheets decreased the expression of the viral G protein, which is in charge of viral attachment, both before and after treatment, suggesting that the GSCC sheets can also directly influence viral gene expression. When combined, these findings unequivocally demonstrate that curcumin's effectiveness against HRSV can be enhanced through encapsulation.

2.5 Transmissible Gastroenteritis Virus

Transmissible gastroenteritis virus (TGV), a pig coronavirus, is another virus that seriously affects cattle and contributes to financial loss in the pork industry. Taking note of curcumin's ability to neutralize other enveloped viruses, curcumin was assessed against TGV. Viral production was decreased by direct incubation with at least 20 µM of curcumin before infection. Moreover, curcumin treatment resulted in a decrease in viral absorption that was dose-dependent. It also decreased the amount of protein at concentrations that weren't harmful to porcine kidney (PD-15) cells and the viral production (IC50 of 8.6 µM).

3 DNA Viruses

3.1 Human Adenovirus

Our team assessed curcumin's anti-human adenovirus (HAdV) properties. Curcumin (0–100 µM) reduced the expression of the viral early 1A (E1A) proteins in A549 human lung adenocarcinoma cells infected with HAdV types 4, 5, or 7, which is necessary for the virus to finish its replicative cycle [80,81], suggesting curcumin is effective against a variety of HAdV types. Additionally, curcumin treatment lowered the number of copies of the HAdV-5 viral genome and the amount of virus recovered as shown by the plaque assay. The most effective curcumin concentrations, however, were only marginally less than the curcumin CC50 (~68 µM) in this cell line, suggesting that curcumin may only have a very limited therapeutic window against HAdV.

3.2 Bovine Herpesvirus

When bovine herpesvirus 1 (BoHV-1) was immediately incubated with 10 μM curcumin, the viral titer was significantly reduced, as determined by TCID50 analysis. Curcumin did not, however, lower the BoHV-1 titer in a binding assay, indicating that it may be influencing internalization rather than preventing viral attachment. When given during infection, 10 μM curcumin considerably decreased the viral titter in Madin-Darby Bovine Kidney (MDBK) cells; but, when injected right after the cells had been incubated with the virus inoculum for one hour, it had no discernible effect. The process of lipid raft generation has been found to be impaired during BoHV-1 infection, leading the scientists to hypothesize that curcumin may be preventing BoHV-1 infection by upregulating it. assessed the efficacy against BoHV-1 of co-encapsulating curcumin and acyclovir, two licensed pro-drugs that block HSV replication, into three microparticle (MP) formulations made of the polymer hydroxypropyl methylcellulose. All three MP formulations dramatically reduced BoHV-1 plaque formation in MDBK cells, more so than any one antiviral test drug at any dose (2.7–203.6 μM).

4. Improvement of Antiviral Activity of Curcumin

Numerous antibacterial qualities of curcumin, including its antiviral qualities, led to its usage in traditional medicine. Curcumin's poor solubility and cell absorption impede the development of drugs based on it, despite its great promise. Curcumin is frequently combined with other organic substances to increase its oral bioavailability. The primary active ingredient of black and long peppers (Pipper nigrum L. and Piper longum L.), piperine, has the capacity to block the glucuronidation of numerous medications and increase the bioavailability of curcumin. In this instance, piperine, black pepper, or long pepper are used with curcumin finished products to increase their consumer appeal. Recently, several methods have been applied to increase the antiviral activity of curcumin.

4.1 Potential of Curcumin as Antiviral Agent

A class of pharmaceuticals used to treat viral infections is known as antiviral medicines. In this case, targeted antivirals work well, although broad-spectrum antivirals work well against a variety of viruses. Antivirals prevent viruses from proliferating, in contrast to antibiotics that eradicate the infection they combat. Antimicrobial pharmaceuticals, such as monoclonal antibody-based antiviral therapies and those with antibacterial, antifungal, and antiparasitic properties, are categorized as antiviral medications. Antivirals can be used to treat infections because it is believed that they are safe for the host. Viral genotype alterations that decrease drug susceptibility led to the development of antiviral medication resistance. In this case, the drugs' effectiveness against the target virus has been diminished or destroyed. Antiviral therapy will surely continue to face significant obstacles due to the fact that resistance has spread to all specific and potent antimicrobials, including antiviral medications. There are a number of obstacles in the way of developing new antiviral drugs, and extensive drug design and validation are necessary. Therefore, investigating the repurposing of already-approved medications or naturally occurring chemicals can offer substitutes for creating brand-new antivirals. In this case, the drugs' effectiveness against the target virus has been diminished or destroyed. Antiviral therapy will surely continue to face significant obstacles due to the fact that resistance has spread to all specific and potent antimicrobials, including antiviral medications. There are a number of obstacles in the way of developing new antiviral drugs, and extensive drug design and validation are necessary. Therefore, investigating the repurposing of already-approved medications or naturally occurring chemicals can offer substitutes for creating brand-new antivirals. One of turmeric's constituents, curcumin, has been shown to have a number of uses in the prevention or treatment of illnesses, including cancer and viral infections.

5. Application of turmeric

Sorano.	Purpose of Usage	Remarks
1.	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
2.	Used in the management of diabetes mellitus:	Turmeric rhizome powder is very useful with amla juice and honey in Madhumeha (diabetes mellitus)
3.	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.
4.	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.
5.	Used in the mitigation of dermatophytic activity:	Rhizomes of Haridra fresh juice have the antiparasitic ability in numerous skin affections.
6.	Used in mitigation of drug resistance:	This is due to the ability of curcumin as a potent drug resistance preventer.
7.	Used as additives in other drugs	This is due to the synergism of Curcumin and other drugs.

6. Conclusions and Recommendations

Curcumin has several benefits in the fight against viruses, fungus, and bacteria. It is a miracle medication because of its synergistic benefits, which include anti-oxidant, anti-inflammatory, and anti-tumoral properties. They may be used to treat and prevent a number of diseases due to their capacity to influence a wide range of molecular targets. Drugs boosted with curcumin show great promise as they can be easily absorbed into the body and have specific antiviral actions. Curcumin's solubility limits its usefulness in treating infectious disorders; however, many methods have been found to increase its potency and, thus, its potential for application in medicine. Curcumin's antiviral properties may be used to combat novel and emerging viruses. It has been found that curcumin's activity is enhanced when it is transformed into bioconjugates, nanoemulsions, nanoparticles, and nanotubes, expanding its potential uses in medicine. Curcumin, too, has been shown to function best in treatments when started early. This suggests that curcumin should be re-motivated to be used in daily meals as preventive medicine to help shield the human body from infections caused by a variety of pathogenic organisms, including viruses. Through a variety of ways, curcumin and its analogues can prevent the replication of a wide range of viruses. Curcumin's usefulness as an antiviral agent is compromised by its low bioavailability and quick metabolism, which may account for the limited success shown in human clinical trials. The creation of novel curcumin-derivates that exhibit higher antiviral activity with lower toxicity as well as ongoing research into such formulations could result in the development of curcumin as a broad-spectrum antiviral for clinical application in humans.

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