

Bioactive Effects of Curcumin in Human Immunodeficiency Virus Infection Along with the Most Effective Isolation Techniques and Type of Nanoformulations

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Abstract: Human immunodeficiency virus (HIV) is one of the leading causes of death worldwide, with African countries being the worst affected by this deadly virus. Curcumin (CUR) is a *Curcuma longa*-derived polyphenol that has attracted the attention of researchers due to its antimicrobial, anti-inflammatory, antioxidant, immunomodulatory and antiviral effects. CUR also demonstrates anti-HIV effects by acting as a possible inhibitor of gp120 binding, integrase, protease, and topoisomerase II activities, besides also exerting a protective action against HIV-associated diseases. However, its effectiveness is limited due to its poor water solubility, rapid metabolism, and systemic elimination. Nanoformulations have been shown to be useful to enhance curcumin's bioavailability and its effectiveness as an anti-HIV agent. In this sense, bioactive effects of CUR in HIV infection are carefully reviewed, along with the most effective isolation techniques and type of nanoformulations available.

Keywords: curcumin, bioactivities, HIV therapy, nanoparticles, nanoformulations

Introduction

Human immunodeficiency virus (HIV) infection is the most critical public health challenge that our society has ever faced. Since the 1980s, 75 million individuals have been infected by this deadly virus, leaving in its path a staggering burden of 32 million deaths.¹ Up until 2016, it was among the top 10 leading causes of death globally.² It remains one of the recurrent and common origins of mortality in the African region, with around 4% of the population infected; moreover, this continent alone accounts for

~70% of all infected cases.³ There are two main types of HIV: HIV-1, which is accountable for the spread of this epidemic, and HIV-2 which is mainly restricted to western regions of Africa.^{4,5} The harming effect of this retrovirus resides in its ability to destroy cluster of differentiation 4 (CD4) T cells, these being responsible for activating adaptive immune responses.⁶ This effect will usually lead to acquired immunodeficiency syndrome (AIDS), usually within the first ten years after diagnosis. This syndrome comprises a vast number of opportunistic illnesses, i.e., infections, malignancies, and specific cases of wasting and encephalopathy.⁷ Before introducing highly active antiretroviral therapy (HAART) in the late 90s, the life expectancy of a patient after the onset of AIDS was around 2 years. Now, with proper treatment, a patient can live for >10 years after this dangerous syndrome onset.⁸ Furthermore, early initiation of antiretroviral therapy (ART) following HIV diagnosis seems to be linked to a higher probability of immune reconstitution to near-normal CD4 cell levels and a dramatic decrease in transmission rates.^{9,10} However, currently available treatment strategies have critical challenges. Antiretroviral therapeutics require a lifelong responsibility, with poor adherence generally resulting in increased viral load and subsequent treatment failure. Also, antiretrovirals exhibit low solubility, resulting in poor bioavailability, and increasing the risk of suboptimal drug concentrations.¹¹ Therefore, nanomedicine has been considered a potential solution to ART bioavailability issues.¹² Nanoformulations can offer a wide range of possibilities in HIV treatment beyond classic ART; additionally, they can also provide the opportunity of using natural or synthetic compounds that can serve as enhancers of conventional therapeutic drugs.

Currently, there is no safe and effective treatment for HIV. Antiretroviral medication, however, can help HIV patients live longer and have fewer secondary infections. Pleiotropic chemicals, which are natural compounds, might be effective against HIV. Because of its activities such as antioxidant, anti-inflammatory, anticancer, antiviral, and antibacterial, curcumin (CUR), a yellow pigment found in the spice turmeric (*Curcuma longa* L.), can be used to treat a variety of disorders, including HIV-AIDS.^{12,14} Unlike other phytochemicals, CUR has been proved to have a wide range of functional activities, i.e. food additive, colorant, antioxidant, and as remedies.^{12,13} In recent years, CUR has received particular attention from the scientific community due to its antimicrobial, anti-inflammatory, antioxidant and immunomodulatory effects.¹⁴ Further, it has proven benefits in neurodegenerative,¹⁵ psychiatric,¹⁶ and cardiovascular¹⁷ diseases, as well as in diabetes mellitus, cancer,¹⁴ autoimmune¹⁸ and infectious diseases, including HIV. Briefly, CUR exerts an anti-HIV effect by acting as a possible inhibitor of gp120 binding, and of integrase, protease and topoisomerase II activities.^{8,19,20} However, its usefulness is somewhat finite due to its low water solubility, rapid metabolism, and rapid systemic elimination.²¹ Nano-particle (NP) formulations could play a key role in enhancing CUR's bioavailability. Nanoparticles (usually 10–200 nm in diameter) can improve the loaded therapeutic molecule's circulation duration and residency at the problematic site by enhancing penetration and retention (EPR), which is a critical feature in drug delivery technology. CUR delivery with nanotechnology not only improves solubility, quick drug metabolism, degradation, and drug stability difficulties, but it should also disseminate or target targeted tissues while reducing inadvertent harm to nearby normal cells/tissues.^{14,19} Several tactics have been used to increase the solubility and bioavailability of CUR as nanotechnology continues to evolve.¹⁷ The use of organic nanomaterials such as polymers, lipids, dendrimers, and polysaccharides with functionalization of targeted therapy has been proposed and explored based on specific purposes or requirements for CUR. The obtained CUR has been efficiently scaled down to nanoscale by using nanotechnologies, which considerably aids in maximizing bioactivities and minimizing physical and chemical degradation of CUR.^{12,20,21} In this sense, this review collates the information on bioactivities of CUR in HIV infection, at same time highlighting the CUR isolation techniques along with the various types of nanoformulations available.

Curcumin: Origin and General Bioactivity in HIV

Curcumin: Origin and Chemical Structure

Turmeric has been conventionally used as a spice and for a number of remedies for centuries.^{22,23} CUR is the major active chemical compound present in turmeric. Belonging to the Zingiberaceae family, turmeric is composed of curcuminoids, which include cyclocurcumin and three types of CUR, present at different percentages, with 77% corresponding to CUR I, 17% to CUR II, and 3% to CUR III.²⁴ In addition, CUR contents differ substantially depending on the different *Curcuma* spp., along with geographical locations that also lead to differing chemical content of CUR, probably due to hybridization of other species; so, it is very important to select the species with higher CUR contents.²⁵ In 1815, CUR (diferuloylmethane) was

obtained by Vogel and Pelletier while its chemical structure, (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (Figure 1) was validated by Lampe and Miłobędzka in 1913.^{26,27}

Despite phenolic compounds have gained increasing attention in the last years for their multiple health-promoting abilities, and CUR is a good example, its numerous pharmacological activities have even boosted towards a deeper knowledge on their therapeutic effects.^{25,28}

Curcumin: Pharmacological Actions, a General Perspective

There is a plethora of research articles supporting the anti-inflammatory, antioxidant, antiseptic, analgesic, antimicrobial (such as antibacterial, antifungal, antiviral, antimalarial) and anticancer properties of *C. longa*, mostly attributed to the chemical compound CUR present in its chemical composition.^{29,30} Generally recognized as safe (GRAS) when consumed up to 12 g/day by the Food and Drug Administration (FDA) for healthy consumption without causing any side effects in humans in a clinical trial,³¹ there are still many turmeric features that need to be better addressed. Table 1 shows the mode of action of CUR responsible for its multiple pharmacological properties.

Curcumin Anti-HIV Bioactivity

CUR regulates the secretion of pro-inflammatory cytokine such as interleukin (IL)-4, 6, 8, and tumor necrosis factor alpha (TNF- α). Further, CUR enhances anti-inflammatory cytokines such as soluble intercellular adhesion molecule (ICAM)-1 and IL-10. CUR helps in reducing the inflammation caused by viruses and bacteria.³⁵

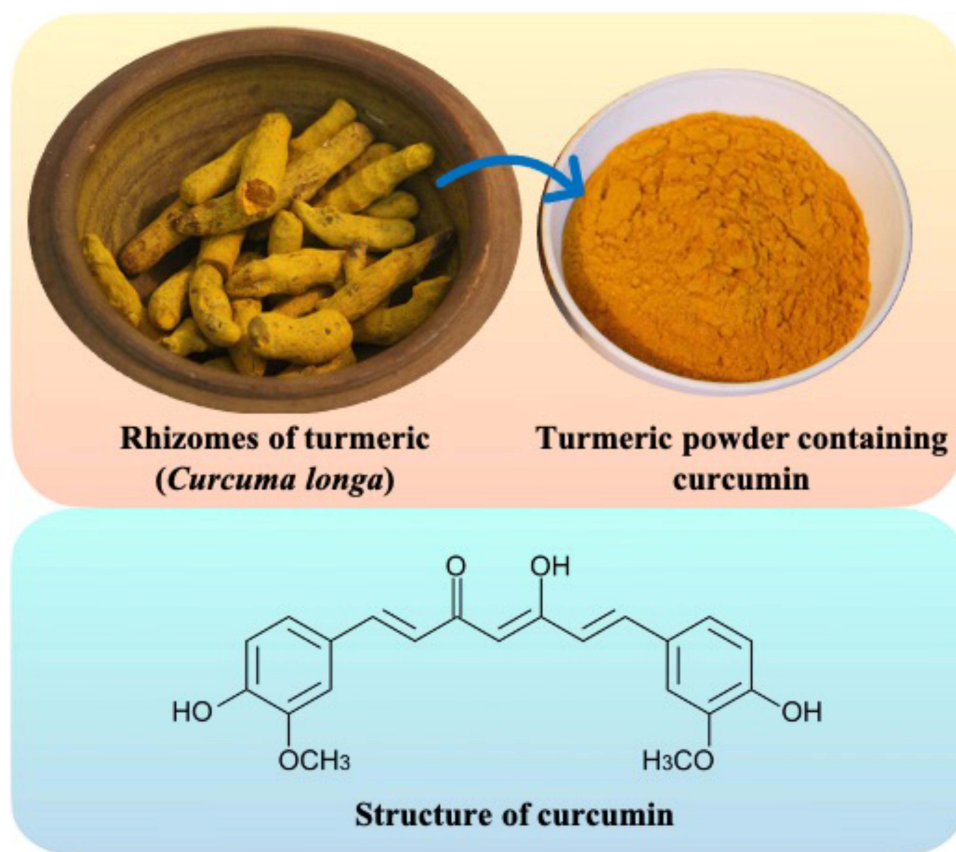


Figure 1 Rhizomes of turmeric and turmeric powder and chemical structure of curcumin.

Table I General Description of CUR Activities

Pharmacological Activity		Mode of Action	References
Antibacterial	<i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermis</i>	Prevents bacterial growth	[32]
	<i>Vibrio</i> spp., <i>Bacillus</i> , <i>Salmonella</i> spp., <i>Staphylococcus</i> spp., <i>Helicobacter pylori</i>	Acts on bacterial cell membrane	[33,34]
Antifungal	<i>Candida</i> spp.	Inhibits <i>Candida</i> adhesion to human buccal epithelial cells (BEC)	[35]
		Develops magnetic interaction with cell membrane, creating disturbance in fungal cell wall	[36,37]
Antiviral	Parainfluenza virus type 3 (PIV-3), respiratory syncytial virus (RSV), feline infectious peritonitis virus (FIPV), vesicular stomatitis virus (VSV), flock house virus (FHV)	Inhibits hemagglutination, virus aggregation and replication	[38]
	Enterovirus	Inhibits virus replication	[39]
	Herpes simplex (HSV)	Reduces HSV-I replication	[40]
	Hepatitis C virus	Inhibits viral entry, suppressing the Akt-SREBP-I pathway	[41]
	Human cytomegalovirus		[42]
	Chikungunya virus, Zika virus	Inhibits virus replication	[43]
	Ebola virus		[44]
	Epstein-Barr virus		[45]
	HIV	Inhibits HIV	[46]
Anticancer	Lung cancer	Activates DNA fragmentation	[39,47]
	Liver cancer	Disrupts human hepatocellular mitochondrial nucleic acid	[48,49]
	Colorectal cancer	Interferes with different biochemical routes involved in cancer cells proliferation	[50]
	Pancreatic cancer	Suppresses nuclear factor (NF)- κ B and signal transducer and activator of transcription 3 (STAT3) activation	[51]
	Chronic myeloid leukemia	Negative effect on metastasis	[52]
	Prostate cancer		[53]
	Breast cancer		[54]
Cardioprotective	Acute myocardial infarction, Atherosclerosis	AMPK, Nrf2, JAK/STAT, NF- κ B, PI3k/Akt, MAPK, Notch, mTOR, PPARs, and arachidonic signaling pathways	[55]
Neurological activity	Traumatic brain injury	Increased expression and nuclear translocation of Nrf2 and enhanced expression of antioxidant enzymes improving the neuroprotective role of curcumin	[56]
Gastrointestinal health	Prevents Diarrhea	Abdominal pain and bloating	[69]

Pathological Perspective

Inhibit HIV-I Replication by Apotransferrin Nano-Particles Provide Efficient Cell Uptake

CUR encapsulation with NPs provides multiple benefits and increases drug solubility, ultimately enhancing its efficacy and stability, and improving drug degradation⁵⁷ and target cells by receptor-mediated endocytosis,⁵⁸ as HIV-infected cells are expressive to transferrin receptors.⁵⁹ CUR-loaded with apotransferrin capsulated in NPs bind to transferrin receptors, leading to cell uptake and T-cells cytotoxicity, eventually inhibiting HIV replication, at the same time also inhibiting the expression of topoisomerase II, interleukin (IL)-1 β and cyclooxygenase (COX)-2 blocking HIV-induced inflammatory activities.⁵⁸

HIV-I Integrase Inhibitor

Enzyme HIV-1 integrase, integrates the HIV virus DNA to replicate further. AutoDock software has been used to run docking, giving data on structural analysis of CUR interactions, revealing that it binds to the HIV integrase, with Asp,⁶⁴ His,⁶⁷ Thr,⁶⁶ Glu,⁹² Thr,⁹³ Asp,¹¹⁶ Ser,¹¹⁹ Asn,¹²⁰ and Lys¹⁵⁹ being the binding sites for integrase. CUR also binds with the active site links the catalytic residues adjacent Asp¹¹⁶ and Asp,⁶⁴ and close to divalent metal Mg²⁺ ion resulting in integrase inhibitory activity against HIV.⁶⁰ For example, a study conducted in Germany testing two CUR analogs, dicaffeoylmethane and rosmarinic acid, stated that both inhibited the integrase activity, at IC₅₀ values <10 µM. The study showed that CUR binds to lysine amino acid at active site of HIV-I integrase enzyme and inhibits its activity.⁶¹ Similarly, a study in the USA showed the inhibition of integrase with IC₅₀ values of 40 µM for strand transfer, causing a deletion of mutant containing amino acids, that ultimately suggests anti-integrase activity.⁶²

Inhibition of Proteases

Computational docking has also revealed that CUR inhibits proteases, through CUR binding to active sites of Asp,²⁵ Asp,²⁹ Asp,³⁰ Gly,²⁷⁰ Asp,²⁹⁰ and Asp³⁰⁰ of HIV proteases and triggering their inhibition. CUR also inhibits proteases of HIV-1 (IC₅₀; 100 µM) and HIV-2 (IC₅₀; 250 µM). Increased number of hydrogen bonding promoted by the hydroxyl and/or keto-enol chemical structures are crucial for the inhibitory action of both HIV-I integrase and protease.⁶⁰

Inhibition of Genome Expression

HIV-1 gene expression depends upon Tat and Rev proteins, which activate the transcription and transport mRNA that encode the viral proteins.⁶³ CUR inhibits Tat protein, reducing HIV infection in an individual. A study reported that CUR (10–100 nM) inhibited Tat activation of HIV-1-long terminal repeats (LTR), 80% in HeLa cells. CUR also inhibits UV-activated HIV-LTR gene expression, an inhibitory effect being found in HIV-Tat protein acetylation by p300 in SupT1 cells, it was thus concluded that it acts as a lead compound in combination therapy of HIV.⁶⁴

Inhibition of Kinases

Kinases have a crucial role in HIV-1 replication. IL-10 production is activated by Tat protein which is activated by protein kinase pathway.⁶⁵ Studies reveal that CUR has anti-inhibitory effect of protein kinase pathway in numerous cells which ultimately is preventative with HIV and also with other chronic conditions.^{64,66}

Inhibition and Degradation of HIV-I Tat Protein

Tat associated with HIV-1 is an intrinsic protein that has a major role in virus replication. This Tat protein is degraded by 20S proteasome. A study showed that CUR degrades Tat protein by activating 20S proteasome, and further inhibits HIV-1 infected cells by decreasing the level of Tat-mediated LTR promoter transactivation.¹⁹ Table 2 and Figure 2 show the CUR action in HIV inhibition.

Hence, the combination of CUR with viral coat proteins, virus-specific enzymes (RNA polymerase, integrase, protease, kinases), may affect and eliminate virus replication, infection, and damage to cells.

Table 2 Mechanisms of Actions of Curcumin

Mechanism of Action of Curcumin	References
HIV-I integrase inhibit	[60–62]
InhibitTat-mediated HIV transcription and replication	[19]
Degradat viral Tat protein	[19]
Inhibit proteases HIV-I and HIV-2	[60]
Interaction with viral reverse transcriptase and integrase (docking data)	[67]
Inhibit HIVI-long terminal repeats directed gene expression	[64]
Inhibit HIV-I replication by apotransferrin nano-particles through provide efficient cellular uptake and target an endocytosis-promoting cellular receptor	[58]

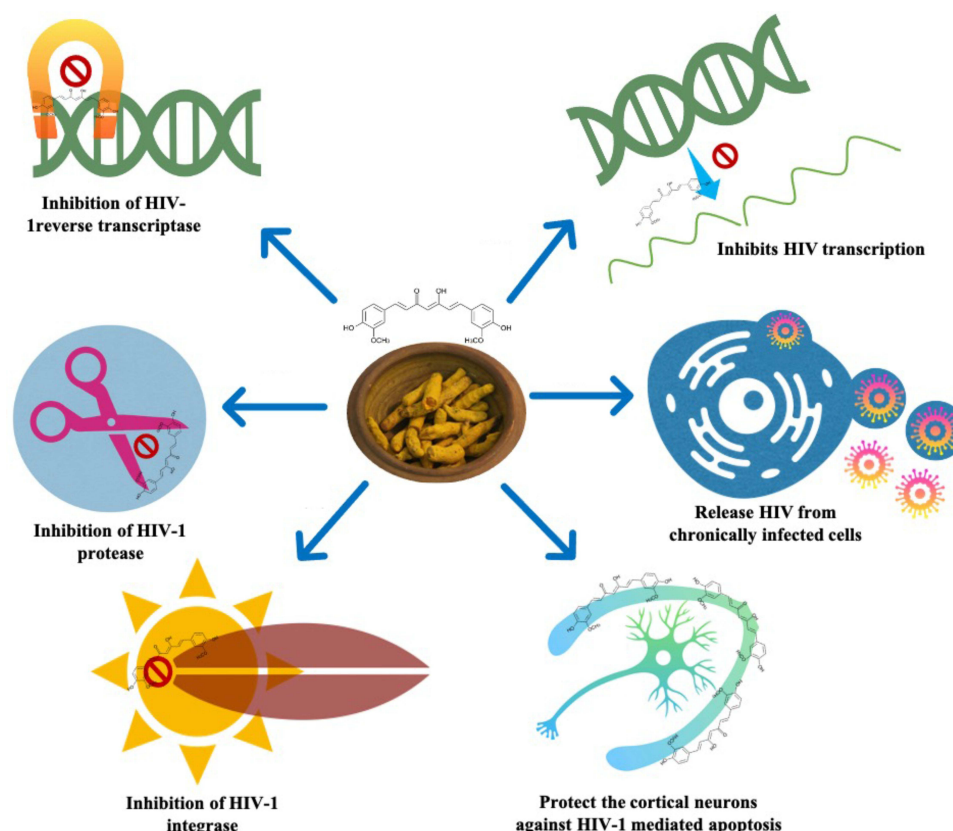


Figure 2 Anti-HIV activities of curcumin.

Activity of Curcumin in HIV-Associated Disease

CUR supplementation to the patients leads to the activation of immune components. This includes reduction in activation of allergy and inflammation and improves the innate immunity to fight against pathogens, cancer, cardiovascular diseases, and other metabolic disorders. CUR can reduce intracellular JAKs/STATs, MAPKs, NF- κ B, β -catenin, and the Notch-1 pathway by regulating the gene expression of pro-inflammatory cytokines, such as IL-2, 6, 10, IL-1 β , TNF- α which mediate inflammatory pathways. CUR has been widely used in the treatment of autoimmune diseases such as arthritis, psoriasis etc.^{38,51} Hence, CUR has been reported to show immunomodulatory effect in the treatment of various diseases. In the following sub-sections the immunomodulatory role of CUR in management of HIV-associated diseases is discussed.

Cardiovascular Disease

The HIV protease inhibitor ritonavir is responsible for causing a plethora of cardiovascular disorders, vascular dysfunction due to oxidative stress, decreased NO level and its release and increased oxygen production. In a study, CUR revealed to be able to block the ritonavir effects, triggering 71% vessel contraction, 59% endothelium-dependent relaxation and 52% endothelium-independent relaxation when compared with control group. Given these findings, CUR inhibits HIV-associated cardiovascular complications at the same time as increasing the lifespan of HIV-infected individuals.⁶⁸

Neurological Disorders

Scientific study showed a positive correlation between HIV-infected individuals and neurological disorders caused by the neuroinflammation and activation of microglia cells of the central nervous system (CNS). CUR exhibited stronger protective action against neuronal damage caused by HIV-1 gp120. CUR reduces neurological disorders by inhibiting

trans-activating proteins (Tat) activated HIV-1 transcription, inhibiting viral replication and also suppressed inflammatory cytokines nuclear factor (NF)- κ B, tumor necrosis factor (TNF)- α , and IL-1 β .^{69,70} CUR also protects the cortical neurons by inhibiting the HIV-1 gp120-induced elevation of the delayed rectification and transient outward K⁺ current.⁶⁹

Gastrointestinal Disorders

Apart from the neurological disorders, cardiovascular problems and carcinogenic complications in HIV immune compromised patients, gastrointestinal disorders are another complicating situation. The prevalence of HIV-associated diarrhea is up to 14%. However, a daily dose of 1.86 g of CUR was able to resolve diarrhea in 13 ± 9 days, alongside a decrease in bloating and abdominal pain complaints as well as weight gain in a few patients.⁷¹

Carcinogenic Conditions

Epstein–Barr virus is most commonly associated with the development of B-cell lymphoma (Burkitt lymphoma, primary central nervous system lymphoma, Hodgkin and systemic non-Hodgkin lymphoma) in HIV-associated immunodeficient patients.⁷² CUR has been reported to act as an efficient anti-cancer and chemo-preventive agent. CUR causes inactivation of Epstein-Barr virus to cause B-cell abnormal growth and necrosis. Moreover, it has been reported that CUR enhances apoptosis of B-cell chronic lymphocytic leukemia (B-CLL) which inhibits the proliferation of Epstein-Barr Virus and thus acts as an important therapeutic agent against carcinogenic conditions.⁷³

Tolerability of Curcumin

The current investigation on the tolerability or toxicity of the CUR showed relatively very low toxicity. Acute toxicity studies showed that 40–100 mg of high doses does not cause any lethal effect on the tested mice. Half-lethal dose for mice was more than 2 g/kg which showed that a safe dose of CUR was high. Majority of investigations showed that CUR is safe (>120 mg/m²) for clinical trials.⁷⁴

Nanoformulation: Molecules, Isolation Techniques and HIV Effects

HIV being a deadly infectious agent, a substantial reduction in mortality rates related to HIV-1 infection has been recorded following application of anti-retroviral therapeutics, it being possible to manage a quickly lethal into a stable manageable illness.⁷⁵ This signifies the utmost importance of bioavailability, pharmacology, cytotoxicity and dosing interval of anti-retroviral drugs for the treatment of HIV infection.^{75–77}

For CUR, the inhibition of HIV-1 infection has been documented.^{78,79} CUR can inhibit HIV-1 transcription,⁸⁰ mainly by Tat-activated HIV-1 transcription.^{80–82} In vitro, it has been observed that CUR can inhibit HIV-1 protease,⁸³ HIV-1 integrase,^{84,85} and in silico binding to HIV-1 reverse transcriptase,⁸⁶ protease,⁶⁰ and integrase.⁶²

On the other hand, oxidative stress has been implicated in a very long list of tissue damage in HIV/AIDS patients for which plant antioxidants can provide defense against viral replication and oxidative stress-associated cell death.⁸⁷ CUR decreases the reactive oxygen species (ROS) and inflammatory mediators' production in microglia (HIV-1-gp120-triggered), thereby protecting cortical neurons against HIV-1-mediated apoptosis.⁶⁹

Nanoformulation sizes can vary from 10–100 nm in diameter and are often administrated per os or by injection as a fluid.⁸⁸ Among their multiple properties, the most prominent one is their useful application in medicine for nano-drugs formulation, helping to reach the target sites promptly.¹⁷ Depending on the preparation method, nanoformulations may have a nano-spheres (drugs are uniformly dispersed) or nano-capsules (drugs are embedded inside the cavity of polymer matrix) structure. Broadly, in terms of size, nano-capsules are larger than nano-spheres and have a greater degree of polymerization; in terms of structure, nano-spheres can more easily be lyophilized in freeze-drying technology than nano-capsules.⁸⁹

Nano-Formulation Techniques and Types

CUR's role in the physico-chemical properties and biological activity of nanoformulations has been suggested by significant progress in the development of delivery systems for CUR. Among the different techniques for nano particles (NPs) elaboration, nano-precipitation is the most commonly used.⁸⁹ The history of synthesizing NPs for medical

purposes dates back long ago based on two principal conventionally produced ideas, one developed by Paul Ehrlich (concept of magical bullets)⁹⁰ and the other by Richard Feynman (concept of miniaturization).⁹¹ Nevertheless, in 1969 it was established that epoxy resin beads can be effectively used as carrier material for the delivering of the drug under physiological pH (acidic and basic conditions).⁹² In an investigation by Müller et al⁹³ working on the development of lipid NPs with wide ranges of application, the surface modified lipid NPs with poloxamine 908 and poloxamer 407 effectively acted as colloidal carriers without being phagocytosed in the system. The study established that lipid NPs can act as a suitable solid carrier for transport of drugs in the vascular system via the blood. In another study, NPs and micro particles were synthesized using a nano-precipitation process.⁹⁴ In this process, nano-form polymer and drug are dissolved at ambient temperature using organic solvent with constant stirring, then stabilizer is solubilized in water at concentration of 0.5–5% w/v. Pouring the organic phase into water phase results in change in the solubility of the drug and a polymer occurs which finally develops the NPs. Finally, the solvent is removed from the system under reduced pressure which is followed by purification using centrifugation and lyophilization.¹⁷

A liposome is a spherical vesicle built from a bilayer of lipids, and is one of the most efficient drug carriers,⁹⁵ and one of the commonly used systems for drugs delivery.⁹⁶ Liposomes are regarded as the most successful encapsulating material to date for targeted delivery of both hydrophilic and hydrophobic drugs by entrapping in its aqueous core and lipid membrane, respectively. Their size varies from 90–150 nm in diameter and they have self-assembling capabilities in the hydrophobic or hydrophilic therapies into its empty core.^{96,97} There are four types of liposomes: (1) conventional type liposomes, (2) polyethylene glycol (PEG) types, (3) ligand-targeted, and (4) theranostic types. Conventional liposomes are composed of a bilayer of lipids which can develop cationic, anionic or neutral phospholipids and cholesterol, surrounding an aqueous core. In conventional liposomes aqueous space and lipid bilayer can be accommodated by water or lipid loving materials, respectively. In PEG type liposomes, the liposome surface is incorporated with the PEG to attain steric equilibrium whereas in the case of ligand targeted liposomes, ligands (antibodies, peptides, carbohydrates) are adhered to the liposome's surface. Theranostic liposomes are a hybrid of all three previously mentioned liposomes which consists of NP along with imaging, targeting and a therapeutic element.⁹⁸ Because of the longer retention periods in the bloodstream, liposomes are viewed as having an advantage in the treatment of disease, with an increasing demand being stated towards liposomal formulations application for drug delivery in medical sectors.

A nanogel (10–100 nm) is made of a hydrogel created under controlled conditions, either by physical or chemical cross-linking of polymer chains. As a result, nanogels are ideal for storing and releasing drugs. As part of this process, cells are prepared and released with active ingredients to retain their activity, improve stability, and reduce drug immunogenicity.⁹⁹ To boost the bioavailability of low-molecular-weight medicines and bio macromolecules in the mouth and brain by means of salt bonds, hydrogen bonds, or hydrophobic interactions, nanogels have been designed as carriers for drug delivery.^{100–102} They are designed to respond to changes in pH, temperature, acidic conditions, the activity of enzymes and magnetic fields, as well as light. Changing the nanogels' conformation may result in a “on-demand” release of any cargo that is placed into the nanogels. If the chemical composition of nanogels is altered precisely, their properties can be precisely controlled.¹⁰³ Khosropanah et al observed that CUR-loaded nanogels were at least twice as powerful as free CUR, presumably due to increased absorption. There is evidence that self-assembled nanogels derived from hydrophobically modified dextrin can be effective CUR nano-carriers, according to literature. It shows that the formulation was more stable in water than in phosphate buffer saline, which was subsequently tested by dynamic light scattering and fluorescence studies.¹⁰⁴

Role of Curcumin Nanoformulations as Anti-HIV Agents

CUR directly binds in multiple target sites related with crucial enzymes of HIV.⁹⁹ An *in silico* study showed that CUR binds to different sites of the substrate-binding cavity of HIV protease.¹⁰⁵ When the cells gets infected, trans-activator of transcription (Tat) is secreted which further promotes the destruction of T-cells and stimulates the formation of HIV-induced tumors. CUR provokes the destruction of Tat by proteosomal degradation and suppressed the Tat acetylation which resulted in reduced HIV proliferation.¹⁰⁶ Similarly, Rai et al described the anti-HIV activity of Cur-AgNP via downregulation of inflammatory mediators (IL-1 β , TNF- α , and IL-6), and stopping HIV replication.¹⁰⁵ CUR combined with silver nanoparticles (AgNP) had been found to act as antiretroviral agents. HIV-1 causes neurological complications

due to its ability to increase the production of pro-inflammatory cytokines.¹⁰⁷ Furthermore, poly-proteins processing by HIV-1 protease may produce new strains of viruses. Consequently, CUR nanoformulations have been shown to be effective in reducing such difficulties because it inhibits the activity of HIV-1 proteases by binding to their active sites, such as the CCR5 (C-chemokine receptor type 5). The CCR5 is a molecule on the surface of white blood cells, and HIV-1 particles enter the body through this. Because of this, CUR molecules attach to CCR5, preventing HIV-1 from gaining access into host cells, and so protecting them from infection. Moreover, CUR's anti-inflammatory qualities block pro-inflammatory cytokines, which contributes to a reduction in HIV-1-related problems even further.^{107,108}

Toxic stress caused by the incompatibility of hard implants with soft brain tissue results in a neurodegenerative reactive tissue response. CUR-releasing softening polymer implants use a new concept of localized CUR delivery and also cause a minimal neuroinflammation provoked by the implant.¹⁰⁵ Additional studies have shown that CUR nanoformulations significantly decreased lipid peroxidation and increased the enzyme and non-enzymatic antioxidants in brain.^{11,109–112} Poly(N-isopropyl acrylamide) and CUR nanoformulations were combined to provide a simple and direct nose-to-brain administration system for the medication.^{111,112} Gandapu et al used sol–oil technology to create apo-transferrin tagged CUR nanoparticles, which have a stronger anti-HIV activity than sol–CUR (IC₅₀ 1.75 M) because of transferrin-mediated endocytosis in T cells.⁵⁸ This can also be attributable to a strong inhibition of HIV-1-induced production of Topo II, IL1, and COX-2, as well as preventing the synthesis of viral cDNA in the gag region.¹⁰⁸ Rai et al also reported that binding of CUR with nanomaterials such as chitosan nanoparticles showed enhanced anti-HIV activity by potentiated obstruction of HIV-1 integrase, which is necessary for the replication of HIV virus.¹⁰⁵ CUR nanoformulations had three times the anti-HIV activity over its free form, and blocked HIV-induced production of IL-1 β , Topo II α , and cyclooxygenase-2 (COX-2), as well as stopping viral complementary DNA synthesis completely.¹¹³

Isolation Techniques for Curcumin

Soxhlet, ultrasonic, and microwave extraction methods are the most commonly used CUR isolation techniques.⁹⁹ Heat is used to target minuscule traces of moisture in plant material in microwave aided extraction. When moisture is heated inside the plant cell by the microwave effect, it evaporates and creates great pressure on the cell wall, causing the plant cell to swell. The pressure presses the cell wall from within, stretching and eventually rupturing it, allowing the active constituents from the ruptured cells to leach out into the surrounding solvent and thereby increasing the yield of phytoconstituents. This phenomenon can be heightened even further if the plant matrix is treated with solvents that have a higher heating efficiency when exposed to microwaves.¹¹⁴ CUR is a thermo-labile compound that degrades after prolonged exposure to microwave radiation. A selective and rapid extraction of curcuminoids from turmeric into organic solvents using the microwave assisted extraction method has been reported, showing 60% extraction of curcuminoids with 75% purity within 1 minute, depending on the solvent used and microwave exposure time. Acetone optimized this process at a power level of 20%.^{115–117} Another study conducted by Najafpour (2016) showed the extraction of CUR from turmeric utilizing formic acid and microwave aided extraction. They reported 45.1 and 82.4 percentage purity of CUR, respectively.¹¹⁸ Although formic acid extraction was quick, its purity efficiency was lower than that of purified CUR extracted via microwave aided extraction. This was most likely due to the breakdown of CUR in formic acid. As a result, acetone has been advocated as a better extraction solvent than formic acid.^{117,119}

Sono-capillarity and sono-poration can promote liquid penetration through channels created by bubble implosion and alter the permeability of cell membranes, respectively.¹¹⁹ Shirsath et al extracted 72% of CUR from *Curcuma amada*, a closely related species of *C. longa* known as “mango ginger”.^{120,121} A green ultrasound preparation technique was created, which proved to be more efficient than batch extraction and had a lower operating temperature than Soxhlet extraction. The acquired yield was much higher, with the added benefit of saving time. Ultrasound-assisted extraction can save energy and time, reduce extraction temperature and solvent amount, speed up energy transfer, enable selective extraction, and boost productivity.^{122,123} The graphic representation of extraction strategies in Figure 1 was prepared by the present reviewers. Conventional Soxhlet extraction is a traditional method for extracting lipids and other non-water-soluble compounds. Soxhlet can even store these compounds while retaining their characteristics. The disadvantages of the Soxhlet extraction technique are numerous, including the fact that it is time consuming, difficult, and requires a large number of organic solvents.¹²⁴ Supercritical carbon dioxide, free of organic solvents, has been established in numerous

countries for the extraction of CUR, oleoresin, and curcuminoids from *Curcuma longa* and *Curcuma amada*.¹²⁵ There are also a few findings on enzyme-assisted extraction, in which pretreatment of turmeric with enzymes such as α -amylase and glucoamylase resulted in a considerable increase in CUR output.¹²⁶

Conclusions and Future Remarks

CUR has been used as a spice in various dishes and as traditional medicine for a long time. It has great medicinal value and is beneficial in multiple diseases. Here, its anti-HIV associated activities were discussed. Data obtained so far underline that CUR acts as an anti-HIV agent by inhibiting integrase, protease and topoisomerases, besides also exerting protective action against HIV-associated diseases, including cardiovascular, neurological and gastrointestinal disorders. The medicinal potential of CUR has just been recognized on a large scale. CUR was found to be a promising medication candidate when its physicochemical properties were modified using nanotechnology. Due to its pharmacokinetic properties, this natural component has already carved out a sizable chunk of the market. Because no substance is completely self-sufficient, there are disadvantages to be considered in this instance as well. There are still a lot of unanswered problems and issues that need to be addressed before it can be deemed an effective drug delivery mechanism. Despite the fact that we already know how nanocurcumin affects HIV, the human dosage is still at a standstill. Clinical trials in higher-order animals should cross-verify the findings of several conceptual preclinical studies. Because there are so few toxicology studies available, it is difficult to tell how effective the actual implementation is. Due to nanodrug toxicity causing DNA damage, allergic reactions, and neuroinflammation, it is necessary and recommended to do extensive and accurate investigations. As a result, the researchers must study if nano-CUR or free CUR can be employed alone or in combination formulations as supplementary medications in order to provide a conclusive report. Researchers should conduct a thorough investigation into the precise implications of nanocapsulated CUR for future therapeutic or chemotherapeutic treatments.

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Disclosure

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