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Review Article

NANO-COMPOSITES OF CURCUMIN: AN ACCOUNT OF SYNTHESIS, ANTICANCER ACTIVITY AND POTENTIALITY AGAINST SARS-COV-2

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ABSTRACT

Curcumin, an important natural compound derived from *Curcuma longa,* is a diphenolic compound. The compound has high medicinal value and shows prospective applications in cancer therapy. It has been found that nano-formulation of curcumin significantly increases its anticancer activity by increasing its solubility, bioavailability, efficient and target specific delivery system. Syntheses of Nano-composite of Curcumin have been reported with different diverse materials like, PLGA, Solid lipid system, magnetic materials etc. This review is an attempt to document design and synthetic strategies of various Nano-Composites of Curcumin, along with their anticancer activity and potentiality against SARS CoV-2 virus (COVID-19).

Keywords: Curcumin, Nano-composite, Synthesis, Anticancer, COVID-19.

1. INTRODUCTION

Natural products are certainly the best type for the variety in chemotype for the finding of novel therapeutics. At present, natural products and their derivatives occupy nearly one-third of the highest selling pharmaceuticals [1-5]. However, the main problem with the natural products based medicine is their low bioavailability in disease treatment [6]. The molecular bulkiness of natural products based medicine impose key challenges in drug delivery, mainly due to *in vivo* instability, poor absorption, hindered bioavailability, along with low target-specificity [7, 8].

Advancement in nanotechnology paved for progress in drug delivery [9], particularly in nanomedicine based drug delivery, where such particles are of key concern [10, 11]. Those nanomaterials can even be engineered in such a way that they would get attracted precisely to unhealthy cells and allow them to treat those diseased cells directly, thereby increasing it specificity, efficacy and decreasing side effects. Nanomaterials usually defined as particles of size ranging from 1 nm and 100 nm [12]. However, particles having size >100 nm showing these unique properties are also considered as nanomaterials. For instance, nanoparticles base on polymers size ranges between 10 nm and 1,000 nm in diameter can have the features expected for an effective and precise delivery with control release [6, 13-15]. The nanoparticles used in nanomedicine are usualy comprises materials at atomic or molecular level; they actually are small sized nanospheres [16]. Therefore, they are free to move in the human body compared to their bulk counterpart.

Polymeric nanoparticles are of great importance and have been studied and tested extensively with natural products. polyethylene glycol (PEG), polycaprolactone (PCL), poly-l-lactic acid (PLA), Poly(lactic-*co*-glycolic acid) (PLGA), are most studied polymers because of the fact that they can be easily functionalized [17]. There are two main types of polymeric nanoparticles; firstly, the nanocapsules which contains a drug filled core covered by a polymieric membrane and secondly, the nanospheres those are porous and the drugs are evenly dispersed in the pores [18].

In this review strategically interesting syntheses of various nano-composites of Curcumin, along with their bioactivity (with special reference to anticancer activity and potentiality against COVID-19 has been discussed.

2. NECESSITY OF NANO-FORMULATION OF CURCUMIN

Curcumin is one of the well known natural compound that has been found to show potential applications in various diseases. It is derived from turmeric *Curcuma longa* (Fig. 1a) and is a diphenolic compound (Fig. 1b). Due to its prospective applications in cancer therapy, researchers across the world are working on increasing the anticancer activity of curcumin using different strategies. It has been found that nanoformulation of curcumin significantly increases its anticancer activity by increasing its solubility, bioavailability, efficient and target specific delivery system.

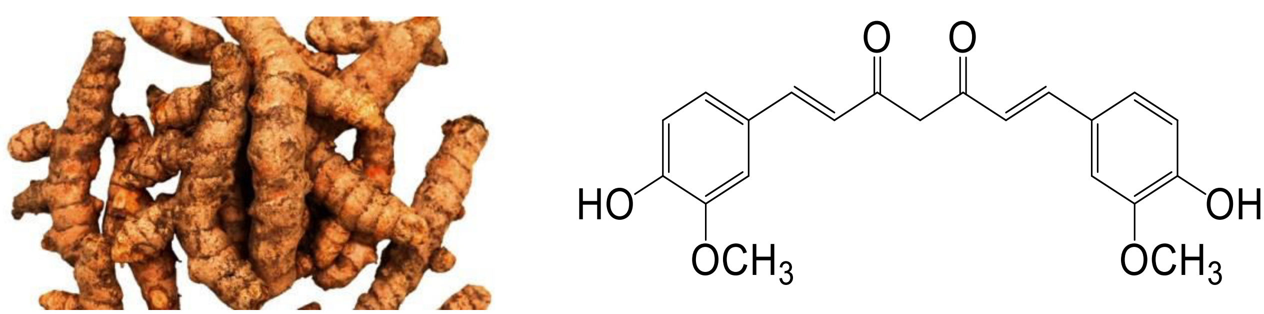
3. STRATEGIES TO SYNTHESIZE CURCUMIN BASED NANO-COMPOSITES

3.1. General synthetic scheme for Nano-formulation of Curcumin

Many researchers have come up with different types of synthetic strategies of curcumin base nano aggregates which help them to increase the potential appilications of curcumin in various fields. Different strategies involves solid/oil/water technique using polyners**,** polymer based nanoprecipitaion, ring-opening polymerization using copolymers, chemical conjugation using cyclodextrin derivatives, magnetic nanoparticles using different metas and polymeric system etc. The general synthetic scheme of nano-curcumin has been outlined in the Fig. 2.

3.2. Important strategies for synthesis of diverse Curcumin based nano-composite

A number of claver strategies have been reported by different groups of researchers to synthesis diverse library of Curcumin based nano-composite. Although most of the noted works have been on Curcumin-Polymer nano-composites, yet many works on Curcumin loaded magnetic nano-particles, Curcumin-B-Cyclodextrin, Curcumin on mesoporous silica etc. have been reported. A comprehensive representation of some of the synthetic methods for Curcumin based nano-composite is presented in Fig. 3.



(a) **(b)**

Fig. 1: (a) Curcumin herb (b) Chemical structure of Curcumin

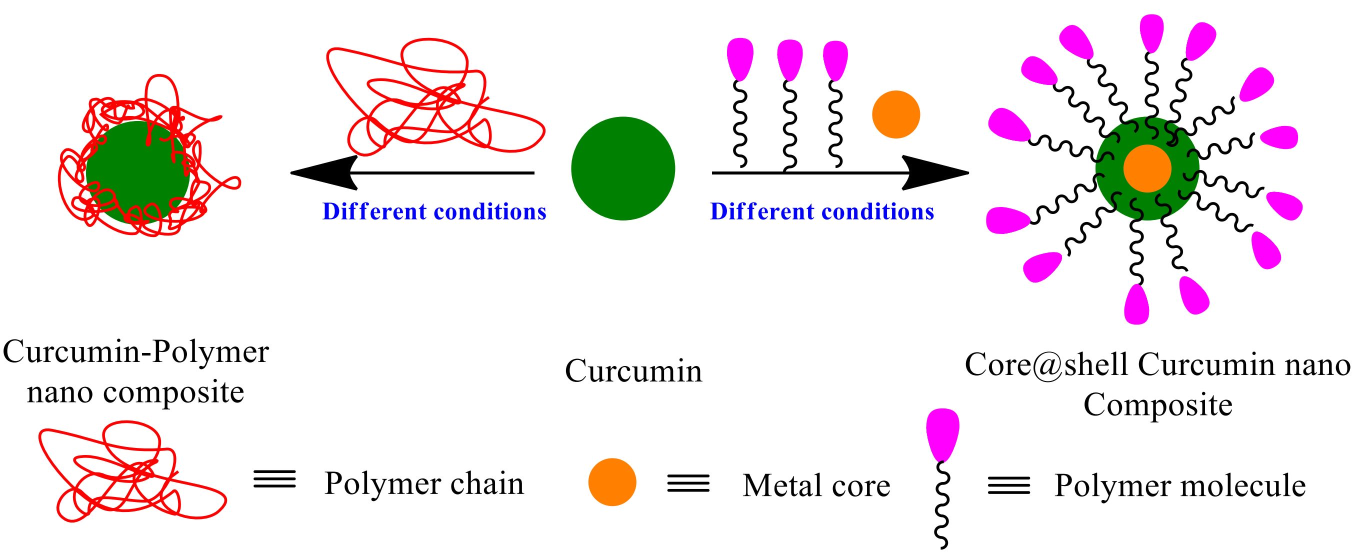


Fig. 2: General synthetic scheme for formulation of Nano-Curcumin

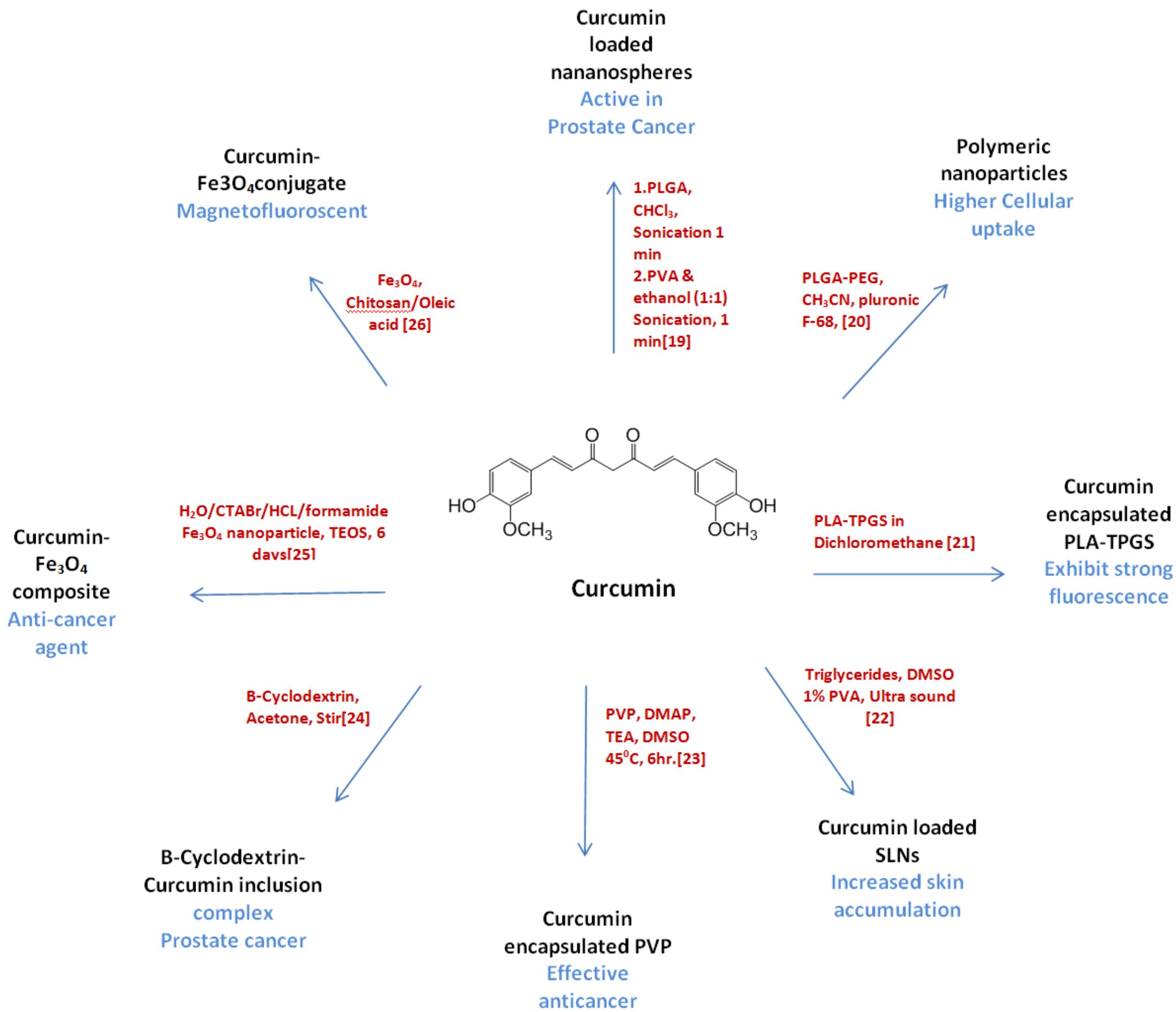


Fig. 3: Different synthetic scheme for Nano formulation Curcumin

Mukerjee et al in 2009 synthesized curcumin loaded PLGA nanosphere by using solid/oil/water technique where they dissolved PLGA in chloroform and free curcumin along with 2% PVA were added and sonicated the mixture for about 1 min. The nanospheres obtained showed a range between 35 nm to 100 nm [19]. P. Anand *et al.* in 2010 also desingned curcumin loaded PLGA nanoparticles by using precipitation technique where PLGA-PEG and curcumin mixed in acetonitrile were added drop wise to an aqueous solution of pluronic F-68 as surfactant and stirred for 15 minutes. The yield was found 95% [20]. Thu Ha *et al.* synthesized nano curcumin by ring opening polymerization method where curcumin dissolved in methanol was added to solution of PLA-TPGS in dichloromethane in a ratio 1:100. The resulting mixture gives the self-assembled micelles of curcumin loaded with PLA-TPGS [21]. Chirio *et al.* reported a synthetic scheme of curcumin loaded SLN (solid lipid nanoparticles) in 2009. In this scheme different types of triglycerides (TG) and free curcumin were heated to dissolve in DMSO, to it slowly 1% PVA was added and irradiated by ultrasound at 25°C [22]. Manju *et al.* in 2010 synthesized polyvinylpyrrolidone (PVP)-curcumin conjugate where they have taken PVP, DMAP and TEA (trimethylamine) and curcumin in DMSO and the mixture was stirred at 45 °C for 6hr. the resulting mixture was collected and PVP-curcumin conjugate was recovered [23]. In 2010 Yallapu *et al.* prepared curcumin encapsulated cyclodextrin (CD) where CD was dissolved in deionized water and to it curcumin in acetone was added and stirred overnight. The resulting mixture was extracted and the curcumin-cyclodextrin inclusion complex was recovered [24]. Chin *et al.* synthesized composite of Fe_3O_4 and curcumin using mesoporous silica capsules in which mixture of

H_2O/CTABr/HCl/formamide was stirred in a high density polypropylene bottle (HDPP) for 2 Days to it curcumin and Fe_3O_4 nanoparticle were added and stirred. The resulting mixture was washed with ethanol and the super magneticnano curcumin was separated [25]. Tran *et al.* synthesized a very interesting nanosized magnetofluorescent Fe_3O_4 and curcumin composite. In this method they have synthesized chitosan (CS) or Oleic acid (OL) coated Fe_3O_4 in which ethanolic solution of curcumin was gradually added. In this way several other types of ferrofluid have been prepared with curcumin [26].

4. CURCUMIN-NANO COMPOSITES: DESIGN AND PROPERTY

Curcumin loaded with PLGA-PVA forming nanospheres are found to act against prostate cancer [19]. Also when it is complexed with cyclodextrin to form a cyclodextrin-curcumin inclusion is finds prospective application in prostate cancer [24]. Curcumin encapsulated with PVA also was found to inhibit various types of cancer [23]. Whereas when curcumin was blended with PLGA-PEG its cellular uptake in different types of cell surprisingly enhanced [20]. PLA-TPGS-curcumin composite have shown strong fluorescence property [21]. Curcumin loaded SLNs have shown increased accumulation in skin than free curcumin therefore, it preventive activity against skin cancer will be higher [22]. It has also been observed that curcumin when complexed with Fe_3O_4 with different polymeric system its property gets changed with different system it acts sometimes as an anticancer drug [25] whereas with another one it shows strong magneto fluorescent behavior [26]. It is evident from Table 1 how variations the nanostructures of Curcumin-nanocomposite, their structures get modified.

Table 1: Different methods of synthesis of Curcumin nano formulation and their size evaluation

Curcumin-nano composite	Methods of preparation	Particle size (nm)	Ref
PLGA	Solid/oil/water emulsion solvent evaporation technique	Mean particle diameter 45nm	[19]
PLGA	Nanoprecipitation technique	89.9 nm (TEM analysis)	[20]
PLA-TPGS	Ring-opening polymerization technique	100-400 nm Small particle ranges from 20-40 nm	[21]
Triglycerides(TG)-Solid lipid nanoparticles(SLN)	Solvent injection technique	250-800 nm	[22]
Polyvinylpyrrolidone cojugate	Chemical Conjugation	15-25 nm	[23]
cyclodextrin inclusion complex	Inclusion Complexation	Small clusters of 50 nm and Self-assembly of 500 nm	[24]
Super magnetic silica reservoirs	Composite	Average Fe_3O_4 core diameter 7.13 nm Ellipsoidal Fe_3O_4-silica composite ranges from 200nm to 1 μm	[25]
Magnetic nanoparticles	Chemical Co-precipitation method	300-500 nm	[26]
Olive Oil	Soil oil Technique	28 nm	[41]
clophosphamide, adriamycin, and 5-fluorouracil	Chemical conjugation		[42]
Nanocurcumin	composite	10 nm	[43]
Nisopropylacrylamide(NIPAAM), with N-vinyl-2-pyrrolidone(VP) and poly(ethylene glycol)monoacrylate (PEGA)	Free radical polymerization process	50 nm	[40]
ϒ-Cyclodextrin-liposomal nanoparticle	Thin film evaporation	67 nm	[37]
PLGA-Anti p-glycoprotein	Precipitation technique	132 nm	[39]
Chitin nanogels	Ultra-sonication	70-80 nm	[44]

5. BIOACTIVITY OF DIFFERENT CURCUMIN BASED NANO COMPOSITES

5.1. Anti-cancer activity of Curcumin based nanomaterials

The use of natural product based nanomedicine finds extensive applications in cancer therapy. The mostly studied and recognizable compound which has been found in combating cancer is Curcumin [27]. Studies have revealed that curcumin induce autophagy which leads to call death [28-31]. Curcumin has a great ability to fight against cancer and it exerts its anticancer activity by various mechanisms which include apoptosis [32-34]. Some studies show that curcumin can be used as to prevent and to treat the cancer cells simultaneously [35]. However, its low bioavailability and poor solubility limits its great potentiality [36]. In this regards, nano-formulations of curcumin has been found to show potential anticancer activity with target specific delivery system, with increased solubility and enhanced accumulation of drug in the cancer cells [37, 38]. Different polymeric nanoparticles also have been reported for encapsulation of curcumin [39, 40].

Recently in 2020, Hanna *et al.* reported preparation of nanocurcumin by sol-oil method and observed strong inhibitory effect of it against proliferation of human Hep-2 cancer cells. Their results have revealed that the cytotoxic effect of nanocurcumin on Hep-2 cancer cells inhibition ensue through G2/M cell cycle arrest and the induction of apoptosis, which was dependent on caspase-3 and p53 activation [41]

Breast cancer one of the most prevalent forms of cancer and researcher across the world are still working onto it. In 2019 a group of researchers have reported a work based on nanocurcumin which has been found to have a relatively high cytotoxic effect on MCF7 breast cancer, and suppresses the expression of cyclinD1, a gene in the development and metastasis of breast cancer [42]. Another work of the same year reported on nanocurcumin exhibiting strong anticancer activity against breast cancer where cancers cells have been treated with nanocurcumin. When studied under microscope, the treated cells showed a visible difference in cell death in comparison to SkBr3 control cells. After incorporation of nanotechnology with curcumin it shows improvement in bioavailability, enhancement in delivery capacity to the target tumor cells and also increases the systematic elimination time after treating the tumor cells [43].

Polymeric nanoparticle encapsulated nanocurcumin using Nisopropylacrylamide (NIPAAM), withN-vinyl-2-pyrrolidone (VP) and Poly (ethyleneglyco) monoacrylate (PEG-A) have been synthesized and found to act against human pancreatic cancer [40].

Potentials of Liposomal curcumins have been tested against cancer models of mesenchymal (OS) and epithelial origin (breast cancer). The 2-hydroxypropyl-ϒ-cyclodextrin/curcumin-liposome complex has shown promising anticancer activity both in vitro and in vivo against KHOS cell line and MCF-7 breast cancer cell line. It has also been observed that curcumin loaded ϒ-cyclodextrin liposomes shows remarkable potential as delivery vehicles for cancer treatment of various tissue origin [37].

Nano-Curcumin prepared by poly (DL-lactide-co-glycolide)(PLGA) nanoparticles(Cur-NPs) in presence of modified pluronic F127 stabilizer using precipitation technique. The surface of Cur-NPs was further conjugated to the amino terminal of anti-P-glycoprotein (P-gp) (Cur-NPs-APgp). The physical properties have been investigated, the cellular uptake with specificity of Cur-NPs and Cur-NPs-APgp were noticed in cervical cancer cell line KB-V1 with higher expression of P-gp and KB-3-1 with lower expression of P-gp, observed using fluorescence microscope and flow cytometry respectively. Cytotoxicity of both the complexes were studied using MTT assay. Therefore the results shows that the Cur-NPs-APgp targeted to P-gp on KB-V1 cell surface resulting improving the cellular uptake and cytotoxicity of Curcumin [39].

Curcumin loaded chitin nanogels (CCNGs) were developed by Mangalathillam *et al.* which was used in the treatment in the melanoma. According to the report this CCNGs has appropriate size and surface properties and also have quite excellent potential for drug loading, controlled release and good skin penetration properties. The anticancer activity of nanogels were observed on human dermal fibroblast (HDF) and A375 (human melanoma) cell lines and the outcome of the experiment shows that CCNGs have a very specific cytotoxicity on melanoma in a concentration of 0.1-1.0 mg mL^{-1} but show less toxicity on HDF cells. These CCNGs due to their good penetration in skin was found to show specific toxicity towards melanoma cells and doesn't harm normal cells. Therefore, this CCNGs find prospective applications for melanoma and other forms of skin cancer through transdermal route which makes the treatment effective [44].

5.2. Antiviral Activity: Potentiality against SARS-CoV-2

Curcumin has found to show preventive activity against various viruses therefore, it could be an option for being used against COVID-19 infection. It has been observed that curcumin act against several viral diseases which includes vesicular stomatitis, flock house virus and respiratory syncytial virus [45]. A virus needs a cellular mechanism for its growth and reproduction as it does not have all the desired enzymes for its metabolism and replication. An antiviral drug should stop the process of replication of viral infection by targeting its different metabolic processes. Curcumin limits viral infection by inhibiting the penetration of viruses, by targeting and attacking the different steps in replication cycle vital for the metabolism and growth of viruses [46].

Curcumin has an efficient binding ability to the receptors and can restrict the COVID-19 virus entry. Spike glycoprotein of SARS-CoV-2 binds with the ACE2 receptor which helps the virus to regulate the viral infection through endocytosis. Therefore, to prevent the virus infection it must be necessary to inhibit the entry of virus to the cell simply by targeting the spike glycoprotein. And it has been observed that by molecular docking that curcumin could bind to the target receptors and can block the entry of the virus [47] It has also been found that curcumin acts as potential therapeutic agent in inhibiting virus by disturbing its replication process. On Vero E6 cells infected by SARS-CoV the effect of curcumin has been studied and the result showed the inhibitory effect of curcumin EC50 was found quite higher on SARS-CoV replication [48].

All types of IFNs play a preventive role against viral toxicities. Numbers of research articles have been published on the effect of curcumin on IFNs in various types of viral infections [49]. Viruses can produce several antiviral cytokines. The IFNs can induce production of IFN-stimulated genes (ISGs). It has been observed that action of carbon dots-curcumin composite can destroy PEDV model of coronavirus reproduction by stimulating the synthesis of ISGs and the cytokines of Vero cells by activating the innate immunity of the host [50].

It has been observed that curcumin can have a preventive activity against pulmonary infection often initiates from SARs CoV infection. The signal regulating expression of various inflammatory cytokines can be inhibited by curcumin through factor-κB and MAPK pathways [51]. Curcumin also have the ability to act against human respiratory syncytial virus (RSV) infection by blocking replication of RSV and the release of TNF-alpha [52].

Studies on some COVID-19 patients have revealed some pulmonary diseases which includes pulmonary oedema which generally results from fluid present in the lungs [53]. SARS CoV infection have often activated protein kinase C (PKC) which induce reduction in the activity of epithelial sodium channels at the pulmonary cells which finally leads to pulmonary oedema [54]. Interestingly it has been observed that curcumin has a preventive application in decreasing inflammation resulting from the fluid present in the lungs of rat under hypoxia and this has been achieved through downregulation pro-inflammatory cytokines leading to reduction in pulmonary oedema [55].

So far various reports have shown that how curcumin is so important in prevention of COVID-19 virus. Researchers across the world are continuing research in this filed as combating newly developing viruses have always been a challenge and there is a growing evidence of preventive activity of curcumin which might be come out of an effective drug against COVID-19 virus. Keeping the antiviral activity of curcumin in mind it can be assumed that the proper formulation of curcumin based drug may leads to an effective and more efficient drug which can be used against COVID-19 virus. Evidences shows that nano-curcumin has always been a better version of curcumin as a drug in various fields, therefore, it might be possible of getting a more efficient curcumin based drug active against SARS CoV-2.

6. CONCLUSION

Curcumin is a naturally occurring compound of high medicinal value. Nano-formulation of curcumin significantly increases its bioavailability and delivery efficiency. Syntheses of Nano-composite of Curcumin have been reported with different diverse materials like, PLGA, Solid lipid system, magnetic materials etc. Thus, design and synthetic strategies of various nano-Composites of Curcumin, along with their bioactivity is reviewed in this paper.

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