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Review Article

A Review on Cuminosides Nanomedicine-: Pharmacognostic approach to Cancer therapeutics

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ABSTRACT
As per various reasearch works, Cuminosides isolated from Rhizome of Syzigium cumini has a potential anticancer activity and extensive variety of Antibacterial, antifungal, antioxidative, anti inflamatory activities with absence of toxicity to normal cells of body. Objctives of this review article to clarify enhanced bioavailability and pharmacokinetic properties, acuumlating and absorbing power of this multitargeted drug Cuminosides in nanoformulation at tumor site. Literature survey of cuminoside nanoformulation. talks about its primary rule in viable disease treatment that it destroys particular malignant cells and minimizes there poisonous quality at tumor site. The hemolytic ratio of this formulation is 2.155% which is in the acceptable range for therapeutic applications. Cuminoside nanoformulation also promote uptake of cancer cells in passive targeting due to Enhanced Permeation and Retention" (EPR) effect. Nanocarriers of Cuminoside is made from ethyl cellulose and methylcellulose which readily release cuminoside into blood circulation by adhering to stomach mucousa. This property is responsible for its better anticancer property and it was initially detected using scanning electron microscopy analysis. Cuminoside nanoformulation also reduces effective dose of cisplatin and radiation to inhibit growth of cisplatin resistant ovarian cancer cells. Cuminoside nanoparticles also enhaces tumor reduction of tumor xenografts via dcreased expression of vascular Endothelial Growth Factor (VEGF) as well as COX2. By selectively choosing particle size, zeta potential, stability and targeting moiety, cuminosides nanoformulations can be targeted to specific cancer cells. Cuminosides in form of nanoformulations has numerous advantages including improved efficacy, tumor targeting, reduced systemic toxicity, compliance and convenience. Now a days cuminoside nanoformulation is considred as Abbreviated New Drug Application (ANDA) or New Drug Applications (NDAs).

Key words: Cuminosides, Anticancer, Antiinflamatory, Nanoformulation, Multitargeted drug, Haemolytic ratio.

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INTRODUCTION

Malignancy is the most common disease around the world. An expected 1,606,670 new malignancy cases and 572,960 deaths happened in 2015 in the United States.[1] While chemotherapy remains a very fruitful weapon to treat malignancy, it is often associated with limitations and side effects. There is possibility of recurrence always and these malignancies can develop resistance to chemo-and radiation treatments. Common natural herbal compounds are broadly concentrated on to take in their particular parts in anticancer activities.[2,3]

Cuminosides is a hydrophobic polyphenolic compound got from the products of Syzigium cumini. Cuminosides is portrayed by an extensive variety of antibacterial, antifungal, antiviral, antioxidative, and antiproliferative exercises.[5-7,9] Cuminosides has shown solid disease preventive action, including avoidance of tumor start, metastasis, and angiogenesis in test creature frameworks, against an extensive variety of tumor cells.[8,10,11] Cuminosides has pleiotropic properties that tweak various targets including proteins (thioredoxin reductase, cyclooxygenase 2 (COX-2), protein kinase C (PKC), 5-lipoxygenase, and tubulin), translation elements, development components and their receptors, cytokines, catalysts, and quality managing cell multiplication and apoptosis.[12–14]

Many *in vitro* experiments exhibit that cuminosides restrains disease cells development (IC_{50}, 50% cell development restraint) at convergence of 5–30 μM[3,4,8,12,14,15] Cuminosides has a great degree safe profile in both creatures and people.[16,17] Furthermore, a clinical study contained 15 patients with colorectal tumor demonstrated the growth was nonresponsive to cuminosides at a day by day measurements of 3.6 g (4 months).[21,22] This study recommended there was no change in tumorigenesis or tumor markers and presumed that while cuminosides shows hostile to disease impacts at a centralization of 5–30 μM for 1 or 2 days, accomplishing these fixations at the tumor site in people not been expert because of cuminosides low bioavailability (Figure 1) and higher metabolic action. Adjuvant cyclodextrin and some protected innovations were at first used to beat this issue.[23–25] Case in point, piperine is very prescribed in light of its inhibitory impacts of hepatic and intestinal glucuronidation, which advanced 154% and 2000% bioavailability in rats and people separately.[26-28] This shows the need of cuminosides exemplification in nanoparticles for disease treatment with conceivable focusing on moieties.[15,18,20]

Literature survey of cuminosides and cuminosides nanoformulation

Cuminosides is a broadly concentrated on atom for various therapeutic applications. A Pub Med inquiry legitimizes cuminosides clinical significance and gives an objective why cuminosides nanoformulations are required for further examination (Figure 2). The database covering Jan. 2008 to Dec. 2015 with watchwords" "cuminosides" in "title and conceptual" exhibits an exponential development of examinations, i.e., more than 3500 studies. The indexed lists for cuminosides based nanoparticle, liposome, nanotechnology, and nanomedicine, uncovers practically nothing. An aggregate of 210 reports depict different parts of cuminosides restorative advantages. These examinations recommend nanotechnology intervened conveyance of cuminosides is in the early phases of advancement. According as far as anyone is concerned, there are just 1 audit articles principally covering cuminosides and its nanoformulations. Our survey concentrates on different sorts of nanoformulations taking into account their basic variability, work, and enhanced

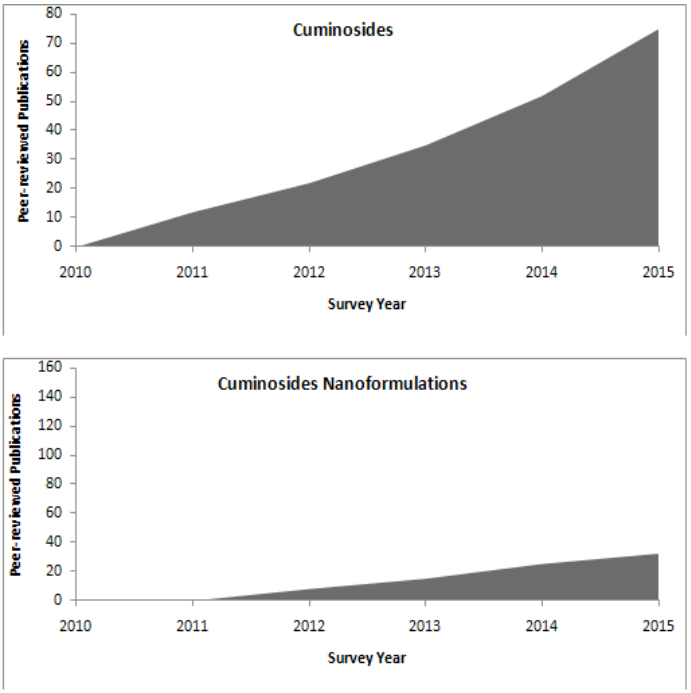

Figure 1: Basic and clinical significance of cuminosides and nanocuminosides formulations in the field of medicine over a ten-year period

The number of peer-reviewed publications was collected using PubMed (data was collected for the 10 year period from Jan. 2001–Dec.

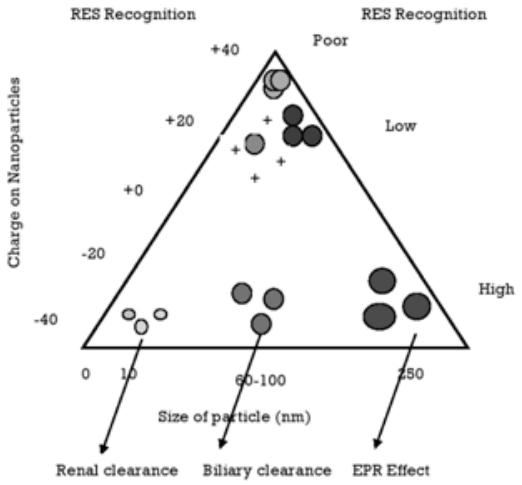

Figure 2: Various clearance mechanisms of cuminosides nanoformulations based on their physico-chemical properties

Note: Reticuloendothelial system (RES) is an older term for mononuclear phagocyte system.

movement.[15] In the meantime, Bansal *et al.*[18,19] present an exceptional survey essentially centered around the chemo-preventive part of nanoformulations and cuminosides stent innovations. Another survey article portrays cuminosides affected components in growth and ramifications of cuminosides nanoformulations in chemoprevention and treatment.[29] As we would see it, to date there is no particular, nitty gritty audit reporting the essential manufactured courses for arrangement of cuminosides nanoformulations, medication stacking wonder and the basic part of nanoparticle uptake by disease cells, anticancer exercises, tissue and bioavailability, and blood similarity. Therefore, this review aims to provide up-to-date contributions of cuminosides nanoformulations to cancer therapeutics; and further, to discuss how novel trends benefit cancer therapeutics.

Cuminoside nanoformulations

Nanoparticle innovation has been generally employed in medicine, including for tumor treatment.[30,31,32] As medication nanocarriers, nanoparticles have a few appealing elements: (i) enhanced epitome or solubilization of remedial medications for defensive and focused on conveyance, (ii) high surface to volume proportion empower alterations to surface useful gatherings keeping in mind the end goal to acquire broad adjustment and disguise, (iii) biocompatibility, unrivaled pharmacokinetics and negligible leeway from body, and (iv) controlled, boosts responsive, remote activation and on interest medication discharge properties. An expansive number of anticancer medication nanoformulations are as of now in clinical or preclinical advancement. A nanoformulations' percentage have been sanction by the FDA are at present accessible in the business sector. A nitty gritty rundown of affirmed plans is accessible.[33-35] Among these, the egg whites bound paclitaxel (PTX) poly (lactide-co-glycolide) (PLGA) nanoformulation (Abraxane™, http://www.abraxane.com/dtc/) is exceedingly effective in expanding the specificity and treatment effectiveness of different cancer(s). Nanoparticle definitions of healthful fixings, for example, carotenoids, co-compound Q10, vitamins (A, D, E, K), phytosterols, minerals, and common concentrates are not new and have been accessible since 1960.[36] The primary rule in viable disease treatment is to accomplish the fancied centralization of helpful specialists at the tumor site to devastate particular malignant cells while minimizing poisonous quality to typical cells.[37, 40]

Cuminosides Encapsulation and Release Characteristics

Cuminosides drug loading is connected with the kind of nanoparticle and preparative system utilized (Table 2). The medication stacking can be controlled by exemplification proficiency which gives the rate of medication added to the definition that exists inside of the nanoformulations. Some estimation routines include isolating the cuminosides nanoparticles from the medium and afterward evaluating the un-entangled or unbound part of cuminosides, giving a roundabout measurement of cuminosides embodied in the nanoparticles.[52] The most much of the time used estimation system is softening nanoparticles up natural dissolvable which brings about an exact cuminosides typified measurement.[41,50] It is fascinating to note that numerous cuminosides nanoformulations beforehand reported has accomplished a stacking limit up to 25 wt./wt. % with 70–99% embodiment productivity. In light of the polymer structure, drug nature and their communications by 3D atomic displaying medication stacking data can be immediately anticipated, minimizing the whole's expense process as well as lessening the time required for the improvement process. The measure of cuminosides discharged from nanoparticle plans is essential since the measure of cuminosides discharge in its dynamic structure is in charge of the restorative impact. In this way, finish medication stacking data and discharge profiles of cuminosides nanoformulations has been introduced in Table 2. A cuminosides typified strong lipid nanoparticle shows a basic Higuchi's square attach model up to 12 h. The discharge profile of poly (butylcyanoacrylate) nanoparticles show 34.74% in 2 h took after by a supported discharge. As per the figured two stages energy mathematical statement: $100-Q=4.5235e^{(-0.1724t)}+4.1641e^{(-0.0114t)}$. A large portion of the nanoformulations follow in vitro arrival of cuminosides in a biphasic design. Cuminosides supported discharge profile may change contingent upon the kind of nanoformulation, synthesis, area of ensnarement and

Table 1: Various approaches to Prepare Cuminosides Nanoformulations, their Composition and Particles Evaluation

Cuminosides Nanoformulation	Method/Technique of Preparation	Composition	Particle Size (nm) and Zeta Potential (mV)
PLGA	Solid/oil/water (S/O/W) technique	30 mg of PLGA polymer, 2% poly(vinyl alcohol) (PVA) and ethanol (1:1) solution, and cuminosides 0.5–2 mg	30–50 nm (TEM)~100 nm (Confocal microscopy)
PLGA	Nanoprecipitation	PLGA–PEG (100 mg), drug (5 mg), and acetonitrile (10 mL) in the presence of 0.1% Pluronic F68	25–75 nm (SEM) 80.9 nm (DLS) −42.4 mV (DLS)
PLGA	Single-emulsion/solvent-evaporation method	20 mg of cuminosides, 4 ml of 5% w/v of PVA solution, and 100 mL of 0.3% w/v PVA solution	77±16 nm (SEM)
PLGA	Single emulsion (o/w)/ solvent evaporation	100 mg of PLGA and 10 mg of cuminosides in dichloromethane and acetone (w/v, 10:1) in the presence of 1% (w/v) PVA aqueous solution.	129.7±9.6nm (SEM) 0.194±0.09 (PDI)
Poly(lactide)-vitamin E TPGS (PLA-TPGS) copolymer	Ring-opening polymerization	Cuminosides solution in methanol was added to the solution of PLA-TPGS in dichloromethane in a polymer ratio of 1: 100	100 to 400 nm (SEM)The small particles are 20–40 nm in size but mm-sized group of several clusters
Soy protein nanoparticles	Isoelectric precipitation and diffusion	Soy protein isolate (SPI) (60 mg/ml) and cuminosides (3 mg/mL) stock solution and cuminosides/SPI ratio of 1:20, 1:50, or 1:100 (w/w)	200–1000 nm (DLS) depending on the ethanol and glutaraldehyde concentrations
Poly(vinyl pyrrolidone) (PVP) conjugate micellae	Chemical conjugation	1.5 g of PVP, 0.5 g of 4-dimethylaminopyridine, 1 mL of triethyl amine, and 100 mg of cuminosides	22.4 nm and 20 mV (DLS) 18.94±4.35 nm (TEM)
α-cyclodextrin (α-CD) derivatives	Chemical conjugation	CD derivatives and their 2:l and 4:1-complexes with Cuminosides	In between 268±16 nm and 692±53 nm depending on the ratios of conjugates and cuminosides
β-cyclodextrin-self assembly	Inclusion complexation and self-assembly	5, 10, 20 and 30 wt.% of cuminosides in β-cyclodextrin	50 nm small clusters to 500 nm self-assemblies (TEM)
Poly(β-cyclodextrin)-self assembly	Inclusion complexation and self-assembly	5,10,20 and 30 wt.% of cuminosides in poly (P-cyclodextrin)	Individual complex or assembly about 50 nm and clusters can reach up to 1 μm (TEM)
Casein micelle	Micelle or complexation	Casein (10 μM) in the presence of 0, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 μM cuminosides	166.3±33.1 nm (DLS) and the same was verified with SEM and AFM
Dextrin nanogels	Self-assembly process at 50°C	DexC16 is composed of a hydrophilic dextrin backbone with grafted acrylate groups, which are partially substituted with long alkyl chains (SC16). DexC16 (0.008 mg/ml) and the cuminosides (10, 30, 50 μM)	61.1 nm in water and 59.2 in PBS solution (DLS) (freshly prepared samples) Size does not change much in 12 days in water (58.7 nm) but in PBS it increases to 100 nm
Thermosensitive polymer nanoparticles	Redox-free radical polymerization	1.8 g monomer, cross-linker (*N*′, *N*′-methylene bisacrylamide), 100 mg PEG-ester, initiator/ activator and cuminosides 20 wt.% loading	~ 132 nm and−1.46 mV (DLS)
Thermosensitive polymer nanoparticles	Free-radical polymerization	Cuminosides (5 mg in 0.1 ml ethanol) and polymer (chitosan-PNIPAM, 50 mg in 5 ml 1% acetic acid) with 100 μl 0.05% TPP solution	100–300 nm (DLS) SEM analysis of cuminosides loaded TRC-NPs revealed a size range of 180–220 nm
O/W nanoemulsions	High-pressure homogenization	Medium chain triacylglycerols (oil), tween 20, and cuminosides	79.5–174.3 nm(DLS)
Sub-micrometer dispersions	Moschwitzer's method by high-speed homogenization	Cuminosides suspensions in water (1%) were subjected to premilling treatments to reduce cuminosides particle sizes to the micrometer range according to Moschwitzer's method by high-speed homogenization at pressure levels ranging from 50 to 200 MPa and for up to 40 HPH cycles	2000, 1000–600 nm (SEM)
Self-emulsifying drug delivery system	Self-emulsification	57.5% surfactant (emulsifier OP: Cremorphor EL, 1:1), 30% co-surfactant (PEG 400) and 12.5% oil (ethyl oleate). It improves cuminosides solubility to 21 mg/g	~ 3.3 nm (DLS)
Nanoprecipitation	Syringe driven filter nanoprecipitation	Cuminosides/ethanol solution with antisolvent water was done in a micromixer [poly(methyl methacrylate)]	The nanoprecipitate first formed as amorphous 30–40 nm nanoparticles, then their amorphous aggregates (~140 nm after 10 min and ~ 200 nm after 90 min), and finally became dendritic aggregates of needle-shaped cuminosides crystals (SEM)

Table 1: cont'd

Nanoprecipitation	Droplet controlled nanoprecipitation	Cuminosides/ethanol solution (0.2, 0.4, 0.8, 1.6, and 2.0 gl−1)	450–210 nm (SEM)
Lipid nanospheres	Vesicle formation	Soybean oil (10 mg/ml) and DMPC:PEG-DSPE (10/1/0.06 molar ratio)	187±53 to 217±93 nm (DLS)
Liposomal formulation	Cuminosides decoration on liposomes using click chemistry	Dipalmitoylphosphatidylcholine/Chol(2:l) liposomes incorporating 10–20% cuminosides conjugate	52.8±5.5 to 207.2±8.0 with zetapotential between −7.6±1.7 and −24.3±1.7mV depending on the liposome modifications (DLS)
Superparamagnetic silica reservoirs	Composite	Fe_3O_4, nanoparticles (37% wt) and cuminosides (30% wt) into the porous silica matrix	Fe_3O_4 core diameter 7.13 nm (variance=l.89 nm) cuminosides shell 2.59±0.07 nm (SAXS) Cuminosides and Fe_3O_4, nanoparticle containing silica particles were ellipsoidal in shape and the size of the particles ranged from 200 nm to 1 μm.
Magnetic nanoparticles	Nanoparticle coating with stabilizer or polymers	Fe_3+/Fe_2+ ratio of 2:1, chitosan or oleic acid	300 nm and 500 nm (DLS and TEM/SEM).
Magnetic poly(lactic acid) microspheres	Oil-in-water emulsion	1% (w/v, 50 ml) of PVA, Fe_3O_4 nanoparticles (5 mg), PLA (50 mg), PEG (20 mg), and cuminosides (5 mg)	0.55 to 0.75 (μm (DLS and SEM)
Hollow capsules	Layer by layer assembly	Melamine formaldehyde templates coated with six double layers of poly(sodium 4-styrene sulfonic acid) and poly(ethylene imine) and 4.5 mg/mg of microcapsules	2.2 to 2.8 μm (DLS)
Silk fibroin and chitosan blend	Capillary microdot technique	Silk fibroin: chitosan with compositions of 100:0; 25:75; 50:50; 75:25)	<100 nm(TEM) 50:50 SFCS (130±4.2 nm) (TEM)
Dendrasome	Diffusion	Dendrosome and cuminosides ratio 25:1	200–500 nm (UV-microscope)
Albumin nanosuspension	Solvent evaporation	Not available	245.2 nm (DLS)

sum. One study recommends that the small scale environment (in fake gastric juice at pH 2.0 and in manufactured intestinal juice at pH 7.4) radically influences the discharge profile. Albeit, beginning discharge in 8 h does not differ much but rather 7 day supported discharge from the nanoparticles discovered ~77% in the intestinal juice and 48% in manufactured gastric juice. Now and again, the system of discharge relies on upon different physical and compound natural conditions.

Cellular Uptake

There is a clear correlation that increased blood circulation time and accumulation of nanomedicine in target tissues improve therapeutic effects compared with free drugs. A stable nanoformulation can be determined by its cellular uptake which is one of the important parameters for drug delivery applications. Like any other nanoparticle mediated drug delivery system, cuminosides nanoformulations also promote the uptake of tumor or cancer cells in passive targeting due to "Enhanced Permeation and Retention" (EPR) effect. (Table 2) illustrates the preferential uptake of cuminosides nanoformulations in various cancer cells. Similarly, some of these formulations show decreased uptake in macrophage or normal cells which suggests the reticuloendothelial system (RES) clearance of nanoparticles is avoided.[51] Such a selective and improved intracellular accumulation or uptake of cuminosides nanoformulations in cancer cells is an indication for a higher therapeutic index.

The extent of cellular uptake of cuminosides depends on the type of nanocarrier, particle size, surface charge, and cell line. For example, polyvinyl alcohol) (PVA) coated PLGA nanoformulations of cuminosides whose particle size varied between~560 to 76 nm (6 formulations) have shown distinctly different uptake patterns.[41] (Table 1) The uptake is continuously increased with a decrease in particle size. This is evidence that low particle size is more easily and highly endocytosized than higher particle size. Additional coating of poly (*L*-lysine) (PLL) on these nanoparticles further increase the uptake due to positive charge which helps in penetrating inside the cells. Numerous reports of various drug nanoformulations support this phenomenon. Researchers[51] have demonstrated that a chitogen based nanocarrier enhances the internalization in MCF-7 and PC-3 cancer cells as time increased from 1 h to 48 h. The cuminosides levels are increased from 0.2 to 0.8% absorbance in UV-vis spectral study. We also learn that the uptake by various cancer cells is quite different and vary formulation to formulation.[50] In a comparative study, PLGA, cellulose, β-cyclodextrin (β-CD), nanogel and dendrimer nanoformulations of cuminosides were evaluated for uptake in SKBR-3, MDA-MB-231 (breast), and HPAF-II (pancreatic) cancer cells.[50] The order of uptake was found as MDA-MB-231>SKBR-3>HPAF-II. It is important to note that cuminosides uptake through nanoformulations is at least 2–3 fold greater than free cuminosides. In another comparative cellular uptake study, free cuminosides diffuse across the melanoma cell membrane and observed fluorescence presence in cytoplasm, localization in the peri-nuclear region and microfilament displacement suggests cuminosides interaction with cytoskeleton proteins. When these melanoma cells were treated with magnetite nanoparticle the fluorescence intensity was lower. The reason was that cuminosides inside the hydrophobic bilayers of the nanoparticles quench the fluorescence property. However, the targeting specificity of cuminosides nanoformulations towards cancer cells can be improved *via* antibody, peptide, penetrating ligand or aptamer conjugation.[15]

After exposure of cuminosides nanoformulations to cancer cells, many nanoparticles were localized in the cytoplasm and inside or around the nucleus,[41,51] longer periods of exposure drastically changed the morphology (e.g., cell lysis and loss of spindle shape) of cancer cells and observed cell debris. This type of behavior is highly dependent upon typical physico-

Table 2: AFM–Atomic force microscopy; DLS-Dynamic light scattering method; DMPC - I, 2-Dimyristoyl-sn-glycero-3-phosphochlorine; PEG-DSPE - I, 2-distearoyl-sn-glycero-3-phosphoehanolamine-N-[monomethoxy poly(ethylene glycol); PLA - Poly(lactic acid); PVA–Poly (vinyl alcohol); SA-L-glutamic acid, N-(3-carboxyl-I-oxopropyl)-, 1, 5-dihexadecyl ester; SAXS–Side angle X-ray spectroscopy; SEM – Scanning electron microscopy; TEM-Transmission electron microscopy

Cuminosides Nanoformulations	Cuminosides Loading	Cuminosides Release	Uptake/Internalization
PLGA	2 mg loading in 30 mg batch of PLGA formulation with 90.88±0.14% encapsulation efficiency	10–13% release was observed within 1 hour and then a sustained cuminosides release of about 65% was noted for 10 days	Robust uptake in DU145, PC-3, and LNCaP cells
PLGA	4 μg/mg of particles encapsulated with 97.5% encapsulation efficiency	Not available	4.5 to 1 fold change with cuminosides and 4.9 to 1.4 fold change with nano-cuminosides formulation in 0 to 60 min incubation in KBM-5 cells
PLGA	7.6 w/w% loading	A biphasic release profile is observed with an initial burst release during the first several hours followed by a sustained uniform release (~65% of cuminosides release in 20 days)	
Dendrosome	4 w/w% loading	Not available	6 fold increased uptake found in A431 cancer cells by dendrosomal cuminosides formulation
Lauroyl sulphated chitosan	Encapsulation efficiency and drug loading content were 50.3% and 9.31%, respectively	16 mg release in 30 days and 82% stable cuminosides in chitosan-CUR formulation for 30 day	Uptake similar to free cuminosides in Caco-2 cells was observed
Alginate-chitosan-pluronic composite nanoparticles	5–10 fold increase in encapsulation in the presence of Pluronic polymer	36% in 12 h, 51% in 24 h and 96 h about 75% of cuminosides determined	No significant difference in uptake detected between cuminosides and cuminosides nanoformulation
Cuminosides/ mono-methoxy poly(ethylene glycol)-poly (ε-caprolactone) (MPEG-PCL)	5–25 % by weight loading with > 97% encapsulation efficiency	About 54.6% cuminosides release found in 9 days	Not available
β-cyclodextrin self-assembly	Loading content in the range of 6.17-26.21 by weight of formulation	80% of cuminosides retention in 6 days in the formation	2–9 fold increase was noticed in DU145 prostate cancer cells
Poly(β-cyclodextrin)-self assembly	The order of loading capacity (μg of CUR per mg of PCD) is PCD5 (48.5) < PCD10 (115.2) < PCD20 (163.4) < PCD30 (223.2)	The order of stability for 72 h found to be PCD30 (~88.7%) > PCD20 (~82.5%) > PCD10 (~77.4%) > PCD5(~71.2%).	3–4 fold increased uptake of CUR was noticed in PCD20 or PCD30 treated prostate cancer cells
Albumin nanoemulsions	The encapsulation efficiency was up to 42.39±0.91% depending on the ratio albumin to cuminosides	96% cuminosides release in 72 h	Not available
Superparamagnetic Silica Reservoirs	A high loading of Fe_3O_4 nanoparticles (37% wt) and cuminosides (30% wt) into the porous silica matrix	The cuminosides entrapped inside the silica capsules diffuses out through passive diffusion processes	Not available
Hollow capsules	4.5 mg of cuminosides/mg of microcapsules	Only 1.11% (0.26 μg/ml) of cuminosides release was observed in 24 h, followed by a sustained release for about 1 week	Not available
Silk fibroin	Up to 96% encapsulation efficiency depending on the ratio of chitosan/silk fibroin/cuminosides ratios	SF formulations released > 0.3 and 0.6 μg of cuminosides in 6 days while chitosan blend composion released only < 0.1 μg	Chitosan-SF-cuminosides formulation exhibited superior uptake in MCF-7 and MDA-MB-231 breast cancer cells
Thermosensitive nanoparticles	Higher loading efficiency and higher affinity of cuminosides noticed between cuminosides and thermosensitive nanoparticles	About 15-25% of the drug is released in about 10 h. Then, a much slower and almost constant release rate is observed.	Up to 2 fold increase in accumulation of cuminosides nanoparticles in PC-3 and L929 cells

chemical properties such as amorphous, crystalline, particle size and morphology and surface charge of the nanoformulations. To study an effective internalization process of cuminosides nanoformulations fluorescence or confocal microscope is commonly employed. These methods utilize the inherent fluorescence property of cuminosides, however, it is interfered with some type of nanoparticles in some cases. Recent investigations also rely on transmission electron microscopy to further validate cuminosides nanoformulations cellular uptake (internalization).[41,51] These investigations provide clear evidence of the presence of nanoparticle internalization at higher magnification. Another convenient method established for the determination of cellular uptake is Prussian blue staining. This method provides both the qualitative and quantitative

Table 3: *In vitro* and *In vivo* Anticancer Potential and Mechanism of Action of Various Cuminosides Nanoformulations

Cuminosides Nanoformulations	*In vitro* Cytotoxicity Profile	Molecular Mechanism	*In vivo* Results
PLGA	IC_{50} (50% cell growth inhibitory concentration) of cuminosides-loaded PLGA nanoparticles was between 20 μM and 22.5 μM while free cuminosides ranged from 32 μM to 34 μM, in LNCaP, PC-3, and DU145 cancer cell lines	Inhibition of NF-κB function	Not available
PLGA	IC_{50} of cuminosides nanoparticles was less than 5 μM in human leukemia (KBM-5 and Jurkat), prostate (DU145), breast (MDA-MB-231), colon (HCT116) and esophageal (SEG-1) cancer cells	Do not induce NF-κB activation expression of cyclin D1, MMP-9, and VEGF	Half-life of cuminosides NPs (2.5 mg/Kg mice) was 1.75 longer than that of cuminosides
PLGA	Nanocuminosides is as effective as cuminosides in HeLa cells, SKBr3, and A549 cells	Increased Annexin V staining Cleaved PARP expression Down regulation of the activation of NF-κB	Not available
MPEG-PCL micelle	IC_{50} of free cuminosides and Cur-MPEG-PCL micelles was 3.95 mg mL^{-1} and 5.78 mg mg mL^{-1}, respectively	Not available	Up to 2-fold increase in CUR concentration was observed in plasma of rats Inhibited the growth of subcutaneous C-26 colon carcinoma in xenograft mouse model
β-cyclodextrin self-assembly	IC_{50} of self-assemblies of cuminosides was 16.8 μM and 17.6 μM (C4-2 cells and DU145 cells, respectively) which is slightly lower than free cuminosides	Increased cleaved PARP expression	Improved CUR levels serum concentrations up to 2-fold (Unpublished data with Subhash Chauhan Lab)
Poly (β-cyclodextrin) self-assembly	Very close IC_{50} values for both self-assembly and free cuminosides in C4-2, DU145 and PC3 cancer cells	The PARP cleavage caused by PCD_{30} is much greater than free cuminosides	Not available
poly(butyl cyanoacrylate) nano-particles	IC_{50} was observed approximately 15 μg/mL for $HepG_2$, Bel7402 and Huh7 cells	Down regulation of COX-2 and VEGF expression	2.2 fold decrease in tumor volume in HepG2 xenograft-bearing mice
Dendrosome	2-fold reduction in IC_{50} with dendrosome cuminosides in WEHI-164 (16.8 μM and 7.5 μM) and A431 cells (19.2 and 14.3 μM) in 24 and 48 h time	Increased Annexin V stain Cleaved PARP (apoptosis)	Tumor growth was significantly suppressed in mice treated with dendrosomal cuminosides
Thermo-sensitive nanocarrier	Formulation showed a specific toxicity cancer cell lines (MCF-7, KB, and PC-3) and non toxic to L929.	Increase apoptosis (PI and Annexin-A binding) Loss of mitochondrial membrane potential	Not available
Folate-modified self-microemulsifying drug delivery system	18.27, 36.69, 30.4 μM and 20.57, 38.59, 25.62 μM in Hela and HT-29 cancer cells for folate CUR-nanoemulsion, CUR-emulsion and free cuminosides, respectively	Not available	In situ colon perfused rats showed absorption of cuminosides increased from 58.41% to 73.38% in 6 h with folate conjugated formulation.
NanoCurc™	IC_{50} ranged between 10–15 μM for BxPC3, ASPC-1, PL-11 and XPA-1	Blocks the activation of NF-κB Downregulation of steady state transcripts of multiple pro-inflammatory cytokines	5 fold increased concentration was observed in pancreas. 3-fold or no growth in tumor was observed in mice with NanoCurc™ in combination with gemcitabine
PEG-chlorestrol	Cm/PEG-cholesterol based cuminosides system showed IC_{50} 1 μM more than free cuminosides	Not available	Not available
NanoCurc™	Almost no growth was observed in DAOY and D283 Med, and the glioblastoma neurosphere lines HSR-GBM1 and JHH-GBM14	Blocked the STAT3 and Hedgehog signaling G(2)/M arrest and apoptotic induction	0.5% of the injected material was localized in the brain
Amphiphilic mPEG-palmitic acid polymer	IC_{50} of cuminosides, 14.32 μM, and nanocuminosides, 15.58 μM, were observed in HeLa cells	*In vitro* enzyme-catalyzed drug release enhances the anticancer activity	Not available

uptake of iron oxide based cuminosides nanoformulations. The uptake of magnetic nanoparticles-cuminosides (MNP-CUR) can be viewed *via* an accumulation pattern of nanoparticles: the accumulation increases as the MNP-CUR concentration increases. The internalized particles are localized in almost every cell and throughout the cell components. This type of nanoformulation showed very minimal uptake by macrophages which supports increased circulation time for a more effective therapy. It is also possible to improve the internalization capacity of this type of nanoparticle by a ligand/antibody/penetrating peptide.

Anticancer Properties

Anticancer properties of each cuminosides nanoformulation depend on the mechanism of specific accumulation or affinity of released cuminosides in cancer cells.[15,20,44] The activity of the same formulation may vary in different cancer cell lines. For instance, the mPEG2000–cuminosides conjugate formulation is active against Caco-2 (colon), KB (oral cavity), MCF-7 (breast), and NCI-H187 (lung) with IC_{50} values in the range of 1–6 μM, similar to that observed for cuminosides itself. The treated cells were much smaller in size when compared with untreated cells and had lost intercellular adhesion.

Nanocarriers made from ethyl cellulose (EC) and methylcellulose (MC)/EC [ECMC] (a blend carrier) readily release cuminosides into blood circulation by adhering to stomach mucosa. This property was initially detected using scanning electron microscopy analysis with *in vivo* experiments. These formulations have shown dose-dependent activity in MCF-7 and HepG2 hepatoblastoma cells. Further, these cuminosides nanoformulations were also applied in the form of lotions (oil in water, water in oil) which preferentially penetrated into porcine skin better than the water nanosuspensions. Recent studies published from our group have demonstrated similar apoptosis characteristics with PLGA, CD assembly, cellulose, magnetic and dendrimer nanoformulations of cuminosides.[41,50] Excessive lysosomal activity or production of vacuoles is responsible for active apoptosis induction in cancer cells by cuminosides nanoformulations as demonstrated by transmission electron microscopy (TEM) analysis.[50,53-55] This activity is infrequently observed with free cuminosides. The primary reason for greater apoptosis is that cuminosides nanoformulations internalize in cancer cells by endocytosis and escape from the phagocytosis, which may result in the release of cuminosides in active form which then efficiently acts on cancer cells. Chen *et al,* have also verified this phenomenon with magnetoplasmonic nanoparticle-loaded drug formulations for such biological activity in HL60 cells. Their TEM results suggest clear characteristics of apoptosis such as blebbing, pyknosis, and damage of cell structure. This phenomenon most likely occurred due to the transport of drug to the nucleus of the cell which induced the activity of the telomerase. A core-shell cuminosides-loaded nanoparticle generated by amphilic methoxy polyethylene glycol-poly (caprolactone) (mPEG-PCL) block copolymers has shown similar effects in a rat C6 glioma cell line[51] Cuminosides encapsulation in a chitosan (CS) and silk fibroin (SF) blend polymer showed significantly lower IC_{50} than SF-encapsulated cuminosides Her2/neu (low and high) expressing breast cancer cells.[44]

Numerous cuminosides nanoformulations have exhibited very similar anticancer potential compared to free cuminosides.[42,39,51,52] This can be explained by the release property of nanoformulations. Many formulations release cuminosides in a sustained manner over a period of 15–30 days. *In vitro* cytotoxicity studies investigate the proliferation of cells in 2, 4 or 5 days. During this time cuminosides release from the formulation is 1/3 that of free cuminosides, yet nanoformulations still exhibit equivalent or slightly greater anticancer potentials. However, their improved efficacy can be observed in long term experiments (such as colony formation)[41,39,42,43,45] as well as in animal model.[38] Cationic poly(butyl) cyanoacrylate nanoparticles coated with chitosan mediated the release of cuminosides efficiently which inhibited tumor growth and tumor angiogensis.[56] Similarly, dendrosomal cuminosides significantly reduced the tumor burden in BALB/c mice models in comparison with void cuminosides and control samples. Additionally, this formulation increased the splenocyte proliferation and IFN-γ production and decreased IL-4 production.[47-49] Liposomal-cyclodextrin formulation of cuminosides promoted autophagic cell death and is highly suitable to treat mesenchymal and epithelial origin cancers.[57] A complex of human serum albumin and cuminosides not only transports 7.7-fold more cuminosides than free cuminosides but also confirms greater therapeutic effect, i.e., up to 66% tumor growth inhibition.[58] Cuminosides nanodisks (disk-shaped phospholipid bilayer formulations) demonstrated a dose-dependent increase in apoptosis through enhanced Fox03a and p27 expression, caspase-3, -9, PARP cleavage, and decreased cyclin D1, pAkt, and Bcl_2 protein.[40] A recent formulation composed of cationic liposome, PEG and PEI complex exhibited 5 and 20-fold increases in the cytotoxic potential against cuminosides-sensitive cells and cuminosides-resistant cells, respectively.[59] This formulation is capable of inhibiting tumor growth 60–90% in mice bearing CT-26 or B16F10 cells.

Most of the tabulated formulations report that cuminosides nanoparticles follow the passive targeting mechanism (Table 3) rather than the active targeting. Passive targeting is a key property of cuminosides nanoparticles and this property promotes the accumulation in tumor(s). Passive targeting may depend on a few important parameters such as particle size, zeta potential, and solubility or dispersion of nanoparticles (Figure 3). Nanoformulations with an optimal size only exhibit EPR effect which in turn increase levels of accumulation in tumor. Additionally, a hydrophilic coating with poly (ethylene glycol) reduces the protein-protein/cells interaction and thereby minimizes the opsonization process.

Folic acid (FA) is a well-known small molecule that binds to folate-receptors and facilitates receptor-mediated endocytosis in a variety of cancer cells and tumors. An optimized formulation of folate conjugated microemulsion (31.1 ± 0.99 nm) comprised of 57.5% Cremophor EL, 32.5% Transcutol, and 10% Capryol 90, increases the percentage of cuminosides absorption from 58.41 ± 7.26 to 73.38 ± 3.12 in the colon of rats.[60] Furthermore, this formulation efficiently targets HeLa and HT-29 cancer cells compared to plain cuminosides and cuminosides loaded microemulsions. A cuminosides-loaded magnetic nanoparticle formulation with transferrin ligand exhibits active targeting of K562 cancer cells (myeloid leukemia). The active targeting of these cuminosides nanoparticles results in significant down-regulation of the Bcr-Abl protein that effectively operates an intrinsic apoptotic mechanism in myeloid leukemia cancer cells. Transferrin-mediated solid lipid nano particles demonstrate selective enhanced anticancer activity against MCF-7 breast cancer cells. This increased activity is due to increased cellular uptake, loss of mitochondrial membrane potential, and generation of excessive reactive oxygen species (ROS). A composite of PVP and hyaluronic acid (HA) cuminosides formulation (six double layers) increased the hyaluronic acid receptor-mediated endocytosis to target cancer cells (glioma cells and Caco-2 cells). Additionally, this strategy also utilizes magnetic property to enhance the internalization. Manju and Sreenivasan demonstrated enhanced efficacy of HA-conjugated cuminosides with folate conjugated gold nanoparticles in HeLa cells, glioma and Caco 2 cells. Similarly, cuminosides nanoformulations conjugated with Tet-1 peptide,[41] apotransferrin and apolipoprotein E (ApoE)-derived peptide have improved the therapeutic value of cuminosides.

A recent pre-clinical study reported for the first time using a targeted Prostate-specific membrane antigen (PSMA) nanoparticle containing the chemotherapeutic docetaxel in patients with solid tumors. This

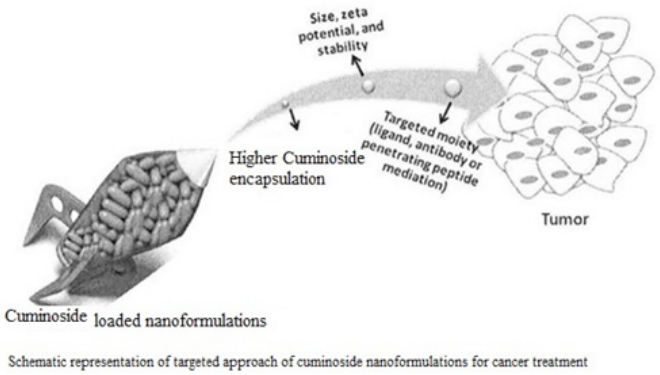

Figure 3: Schematic representation of cuminoside nanoformulation for cancer treatment

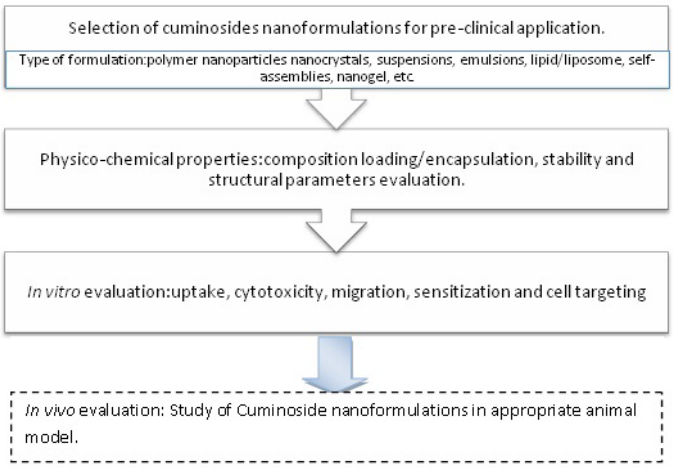

Figure 4: Schematic flow chart delineates the step by step process for the selection of cuminosides nanoformulations for clinical applications

formulation was developed from a combinatorial library of more than 100 compositions varying in particle size, drug loading and release, targeting efficiency and surface modifications. This further supports the premise that effective cuminosides targeted nanoformulations can be developed for treatment of prostate cancer.[15,20] Monoclonal antibody mediated delivery would improve targeting and binding efficacy to cancer cells which would significantly improve the cuminosides anticancer activity. A number of monoclonal antibody conjugation techniques already exist for this purpose[32,41,45,50]

Reversal of Multi Drug Resistance

Drug resistance or multidrug resistance is a phenomenon whereby tumor cells become resistant to primary anticancer drugs. Cuminosides is known to sensitize cancer cells to chemo/radiation therapies. Therefore, cuminosides nanoformulations will have great therapeutic impact in cancer treatment. In our study, cuminosides pre-treatment effectively induced chemo/radio-sensitization and considerably reduced the effective dose of cisplatin and radiation to inhibit the growth of cisplatin resistant ovarian cancer cells (A2780CP).[58] This property can be induced more effectively using Nano-CUR with antibody conjugation capability. Co-encapsulated cuminosides (CUR) and doxorubicin (DOX) in poly (butyl cyanoacrylate) nanoparticles prompted the highest drug resistance reversal and down-regulation of P-glycoprotein expression in MCF-7/ADR cell lines. A new attempt has been made to leverage the

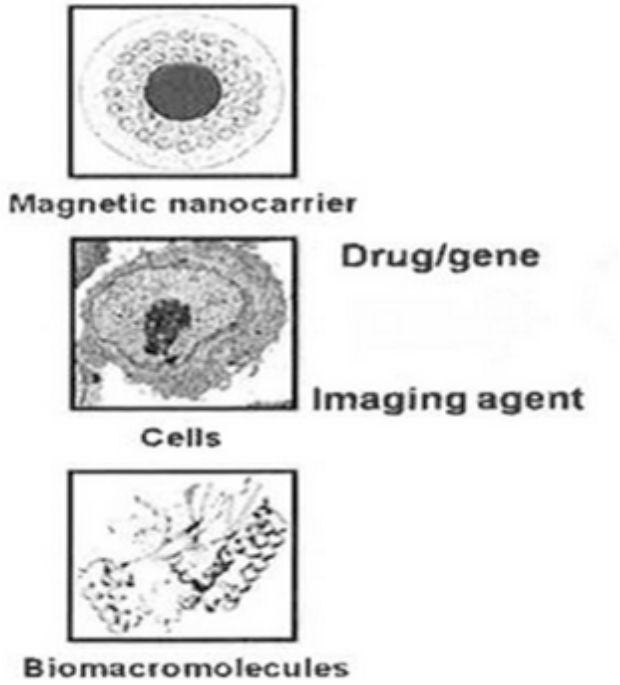

Figure 5: Drug and Gene delivery targeted binding and and separation magnetic resonance imaging,targeting 3D cell culture. Magnetic cuminosides nanoformulations for theranostic and multi-functional applications

therapeutic benefits of PLGA-CUR formulation in rats. This study illustrates that a hypoxia condition considerably reduces the particle endocytosis and localization thereby lower tissue levels of cuminosides are required compared to normoxic conditions. Such phenomenon can be altered by surface modification of nanoparticles. Similarly, cuminosides and doxorubicin co-encapsulation in a lisosomal formulation supports the greater *in vitro* anti-tumor activities against A549 cells compared with that of free DOX. A combined CUR/DOX nanoformulation would also facilitate the retention of DOX in the nucleus for a longer period of time as well as inhibit the expression of MDR1 and BCL-2 at the mRNA level in K562 cells. It is also true that when co-administered, cuminosides and paclitaxel nanoformulations open up the drug resistance in cancer cells. SKOV-3(TR) human ovarian adenocarcinoma cells showed less growth with combination treatment and this co-therapy successfully inhibited the NF-κB activity and down regulated P-glycoprotein.

Pharmacokinetics and Bioavailability

Bioavailability is one of the key pharmacokinetic properties of a drug molecule. This behavior mainly depends on the solubility, stability, metabolism, and degradation of drug molecules. Drug bioavailability follows the administration route: intravenous > intramuscular > subcutaneous > oral > rectal > inhalation. Bioavailability of cuminosides indicates the extent of active compound that reaches the systemic circulation which is readily available at the site of action. Extensive research on *in vivo* investigations of cuminosides nanoformulations is still limited. *In vivo* pharmacokinetics demonstrated a 9-fold increase in oral bioavailability compared to a cuminosides combination (cuminosides with piperine). Cuminosides oral bioavailability was significantly improved with different compositions of various formulations using stabilizers or adjuvant. For this experiment, 250 mg/kg equivalent cuminosides was administered using oral gavages to male SD rats. The order of bioavailability was found to be: cuminosides formulation of milk > aqueous

Table 4: Pharmacokinetics Properties and Bioavailability of Various Cuminosides Nanoformulations

Cuminosides Nanoformulations	Comment
MPEG-PCL micelles	T_{max} (min): 5 and 5 t(l/2) (time): 34.2 and 19.6 AUC(0/t) (mg L^{-1} min^{-1}): 47642.1 and 7933.2 AUC(0/N) (mg L^{-1} min^{-1}): 47864.6 and 7944.6 Cmax (mg mL^{-1}): 430.5 and 305.7 for cuminosides and micelle-cuminosides, respectively
Dibenzoylmethane (DBM) nanoemulsion	3-fold increase in oral bioavailability
Curcurain-loaded solid lipid nanoparticles (C-SLNs)	Cuminosides levels in plasma were significantly increased i.e., 39 times at 50 mg/kg; 155 times at 1 mg/kg; and, 59 at 12.5 and 32 times at 25 mg/kg, respectively
PLGA	Nanoformulation significantly increased the retention time of cuminosides by 96% in the cerebral cortex and 83% in the hippocampus
Cuminosides	$C_{(max)}$ for 150 and 210 mg: 189 ±48 and 275±67 ng/ml AUC (24 h) for 150 and 210 mg: 2,649±350 and 3,649±430 ng/ml×h t(l/2) for 150 and 210 mg: 9.7±2.1 h and 13.0±3.3 h
Nanosuspension	Area under the curve in plasma: 3.8-fold greater than cuminosides the mean residence time: 11.2-fold longer than cuminosides
(PLGA-PEG-PLGA) copolymer nanoparticles	AUC ((0-infinity): 1.31 fold greater than cuminosides t(l/2α), t(l/2β): 2.48 and 4.54 fold increase than cuminosides Mean residence time: 2.67 fold longer than cuminosides

AUC: Area under the curve, C_{max}: Peak concentration, (T_{max}): Time to peak concentration, (t_{lag}): Absorption lag time, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the test (e.g. generic formulation) to reference (e.g. innovator brand formulation).

suspension > micronized suspension > piperine > nanosuspension ≥ amorphous solid dispersion > inclusion complex (HP-β-CD). 200–500% enhancement of the cuminosides area under the curve (AUC_{0-t}) and maximum concentration (C_{max}) was observed with the nano-suspension and inclusion complex (HP-β-CD). A brief summary of important formulations that significantly improved the pharmacokinetics and bioavailability is available in Table 4.

The hemo-compatibility is an index for therapeutic formulations that are immediately exposed upon administration in blood. Accessing their hemo-compatibility in animal or human blood would enhance translation of cuminosides formulations from "bench to bed site". A recent study suggests that PLGA, CD, cellulose, nano-gel, and dendrimer based cuminosides formulations did not show any erythrocytes damage or occurrence of thrombus.[50] Similar observations were made with intravenous PLGA nanosuspensions, cuminosides conjugated nanoparticles, gold-cuminosides nanoparticles, and a layer-by-layer self-assembly cuminosides formulation.[61-65] Rejinold *et al.* demonstrated the biocompatibility nature of a thermosensitive cuminosides formulation by hemolysis assay.

Challenges to Cuminosides Nanopharmaceuticals

We provide a schematic layout which proposes the basis upon which cuminosides nanoformulations can be selected for future clinical application or clinical trials (Figure 4). Liposomal formulations of drugs (Doxil, Myocet, Ambisome, and Depocyt), contrast imaging agents (gadolinium and iron oxide nanoparticles), PLGA formulations of paclitaxel (Abraxane), nanocrystal technology, nanomorph, nanoedge, nanopure, crititech and nanocochleate technologies are currently available in the market. Cuminosides formulations developed by following these principle technologies would benefit from obtaining early approval from the FDA provided evident appropriate science, characterization tools, purity, stability, toxicity, safety profiles along with benefit to human health. However, cuminosides formulations are considered to be as Abbreviated New Drug Applications (ANDAs) or New Drug Applications (NDAs). FDA is also authorized to inspect and examine records to nanotechnology, monitor the post-market safety and identify adverse events reporting. Based on such criteria FDA can pose ban if it is necessary.

Our laboratory is interested in identifying hybrid nanocuminosides formulations that can be applied for multi-functional applications in cancer therapeutics. Currently, we have developed theranostic cuminosides nanoparticles that combine therapy and diagnosis in one platform.[45] Such type of nanoformulation allows loading therapeutic drug(s), biomacromolecule(s) and diagnostic agents and provide not only real-time monitoring of therapeutic outcome but also offers stimuli therapeutic strategies (Figure 5). Overall this review highlights important contributions and issues associated with cuminosides nanoformulation translations for clinical use in the future. It also provides enormous opportunity for implementation of nanotechnology in cuminosides delivery to cancer cells efficiently. Evidence of superior anticancer properties exist for all the strategies but further developments of these cuminosides nanoformulations should follow commonly employed good laboratory and manufacturing practice (cGLP and GMP) using FDA approved compounds. Suitable cuminosides nanoformulations can then be chosen based on appropriate priorities established for both the development of nanotechnology and subsequent therapeutic application.

CONCLUSION

Cuminosides showed excellent anticancer properties yet its inherent poor solubility, higher metabolic activity and poor pharmacokinetics properties hamper its ability to emerge as a potent medicine for cancer. In addition, since cuminosides is a natural compound, there would be some regulatory and intellectual property right issues in regard to using cuminosides as a drug. However, through developing proper formulations, i.e., nanoformulations are possible to get approval. Nanoparticle technology of cuminosides is one of the frontier areas in medicine which will improve human health care. Interest in this area has been emerging worldwide over the last few years. Cuminosides nanoformulations may offer numerous advantages including improved efficacy, tumor targeting, reduced systemic toxicity, compliance and convenience.

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CONFLICT OF INTEREST

The Authors declare that they have no conflict of interest in this manuscript.

ABBREVIATIONS USED

EPR: Enhanced Permeation and Retention; **ANDA:** Abbreviated New Drug Application, **IC_{50}:** Inhibitory concentration; **MNP-CUR:** Magnetic nanoparticles-cuminosides, **PLGA:** Poly lactic co glycolic acid, **BCL-2:** B Cell lymphoma; **MDR1**: Multi Drug resistance 1; **PSMA:** Prostate-specific membrane antigen.

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