Review Paper:

Antioxidant and anticancer activity of nano lycopene

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Abstract

Lycopene is a phytochemical found in various plants, algae and fungi; the most common lycopene source is tomato. Lycopene has been shown to have various biomedical activities such as antimicrobial, anti-inflammatory, anticancer and antioxidant activity. The major drawback of lycopene is its insolubility in water which leads to less bioavailability of the component. Nanoformulation and nanoencapsulation are fields of nanotechnology that aim to improve the bioavailability of many natural compounds and enhance stability.

To overcome the limitation of lycopene, various nanoformulations of lycopene are used and studied for its biomedical activity. Scientists have done multiple researches on nanoformulation of lycopene to improve its availability at targeted sites and to enhance the biomedical activity of lycopene compared to free lycopene. This mini review discussed the recent findings of nanoformulated lycopene and their anticancer and antioxidant activity.

Keywords: Lycopene, Nano lycopene, Antioxidant activity, Anticancer activity.

Introduction

Oxidative stress is caused due to various external and internal factors that lead to imbalanced production and accumulation of oxygen reactive species (ROS) in tissues and cells. This accumulation of ROS causes various diseases such as diabetes mellitus, cardiovascular disease, neurodegenerative disease, cancer etc.[16,28,30] There are various phytochemicals abundant in fruits and vegetables which we are using in our day-to-day life. Most of them have different functional aspects such as antimicrobial, anti-inflammatory, antioxidant, anticancer etc. like vitamins, enzymes, polyphenols and plant extracts (vitamin-C, vitamin-K, Myricetin, quercetin, kaempferol, catalases, superoxide dismutase, glutathione peroxidase)[1,7,11,37].

A phytochemical present in tomatoes is lycopene (LYC). LYC is a carotenoid hydrocarbon that gives a red color to the tomatoes and it is also found in other vegetables and fruits like papaya, grapefruit and carrot[20]. It has been shown to have a prominent free radical scavenging property and also has anticancer activity[17,32]. The major drawback of this component is its low bioavailability. To overcome this, different forms of nanoformulations are being used to enhance the bioavailability, solubility and improve the stability of LYC[11]. Nanotechnology is an emerging field of science that has promising applications in medical sciences which deal with particles under the size of 1000 nm[39] and which help in improving the bioavailability of various phytochemicals.

Some of the applications of nanotechnology in medical science are targeted drug delivery, imaging, theranostics, biosensing etc.[8,12,15,26] Scientists have nanoformulated various phytochemicals with various nanoparticles such as liposomes, solid lipid nanoparticles, lipid-polymers hybrid, nanosphere, micelles etc (Figure 1).[13,19,33] In this mini review, we are going to discuss the recent studies on antioxidant and anticancer activity of nanoformulated LYC.

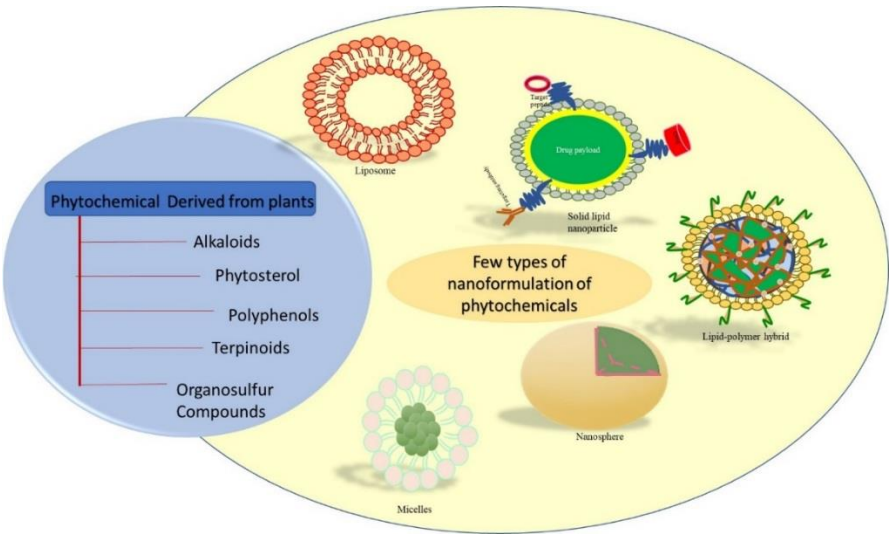

Figure 1: Various types of phytochemicals and their nanoformulations

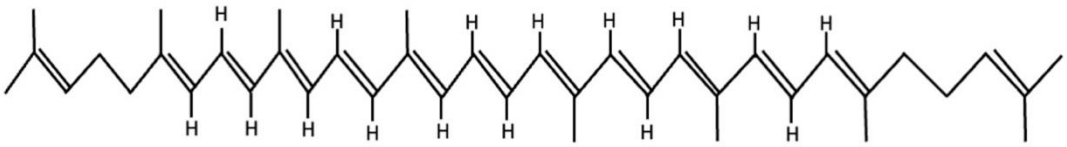

Figure 2: Structure of Lycopene

Structure of Lycopene: LYC is a carotenoid which is bright red in color and water-insoluble in nature. It is synthesized by various algae, fungi and plants. LYC has 35-40 carbon atoms with a tetraterpene (large unsaturated hydrocarbon chain) (Figure 2) and its chemical formula is $C_{40}H_{56}$. Its melting point is 172°C and its boiling point is 660.90°C. Its bright red color is due to the conjugation of many carbon double bonds and LYC is used as a food coloring agent due to its intense red colour[31].

Antioxidant activity of nano lycopene: Lycopene is the most potent antioxidant among the carotenoids which can deactivate ROS. In comparison to alpha-tocopherol and beta-carotene, lycopene has two to ten times higher ability to remove singlet oxygen[17]. Mishra et al[24] studied the antidiabetic and antioxidant activity of nanoformulated LYC in albino Wistar rats. LYC is nanoformulated using the nanoprecipitation method and the polydispersity index and mean size were found to be 100 ± 4.50 nm and 0.04 respectively. The *in vitro* drug release showed that the amount of LYC nanoformulation after 120 min was 93.9% whereas for only LYC it was 32.52 %. In the animal model (female albino mice), the nanoformulated LYC was shown to decrease the blood glucose level. After 21 days post-treatment with nanoformulated LYC, the glucose level was 216.83–106.5 mg/dL and 216.83–101.16 mg/dL when the drug was administered orally at concentrations of 25 mg/kg and 50 mg/kg respectively.

In free LYC (100 mg/kg) treatment group, the blood glucose level was 216.83–98.67 mg/dL. This shows that nanoformulated LYC is more effective in reducing the blood glucose level with a lower dose of drug. The antioxidant activity of nanoformulated LYC and LYC was studied and the values of glutathione (GSH), glutathione–S transferase (GST), glutathione peroxidase (GPx), catalase (CAT) in liver and kidney and superoxide dismutase (SOD) levels present in the liver in the normal control, diabetic control, treatment with LYC and nanoformulated LYC were then observed. In normal control, the level of GSH, GST, CAT, SOD was 125.83 ± 4.85nM of DTNB conjugated/mg protein. For diabetic control, 125.83 ± 4.85nM of DTNB conjugated/mg protein, 6.16 ± 1.24 µmol of CDNB-GSH conjugated formed/min mg^{-1} protein, 69.83 ± 8.33 µmol of H_2O_2 consumed/min mg^{-1} protein, 6.33 ± 1.82 U min/mg Hb^{-1} in erythrocyte in the liver and kidney 115.33 ± 8.06, 5.66 ± 2.30 µmol of CDNB-GSH conjugated formed/min mg^{-1} protein, 36.83 ± 4.64 µmol of H_2O_2 consumed/min mg^{-1} protein respectively. In LYC (100mg/kg) treatment group, the level of GSH, GST, CAT and SOD was 111.66 ± 5.64nM of DTNB conjugated/mg protein, 4.5 ± 1.58 µmol of CDNB-GSH conjugated formed/min mg^{-1} protein 59.66 ± 4.12 µmol of H_2O_2 consumed/min mg^{-1} protein, 5.16 ± 1.80 U min/mg Hb^{-1} in erythrocyte in the liver and kidney 68.33 ± 5.58, 3.83 ± 1.24, 5.66 ± 1.82 µmol of CDNB-GSH conjugated formed/min mg^{-1} protein 24.16 ± 3.22 µmol of H_2O_2 consumed/min mg^{-1} protein.

For nanoformulated LYC treatment (20 mg/kg), the level of GSH, GST, CAT and SOD was 123.33 ± 6.71 nM of DTNB conjugated/mg protein, 5.5 ± 1.38 µmol of CDNB-GSH conjugated formed/min mg^{-1} protein, 66.16 ± 8.06 µmol of H_2O_2 consumed/min mg^{-1} protein, 4.83 ± 1.95 U min/mg Hb^{-1} in erythrocyte in the liver and kidney 84.33 ± 4.94, 4.83 ± 1.35 µmol of CDNB-GSH conjugated formed/min mg^{-1} protein, 31.83 ± 4.54 µmol of H_2O_2 consumed/min mg^{-1} protein respectively. For nanoformulated LYC treatment (50 mg/ml), the values are 124.33 ± 3.40 nM of DTNB conjugated/mg protein, 5.33 ± 1.02 µmol of CDNB-GSH conjugated formed/min mg^{-1} protein, 67.83 ± 8.06 µmol of H_2O_2 consumed/min mg^{-1} protein, 6.16 ± 1.95 U min/mg Hb^{-1} in erythrocyte in the liver and kidney 85.33 ± 6.03 nM of DTNB conjugated/mg protein, 5.16 ± 1.95 µmol of CDNB-GSH conjugated formed/min mg^{-1} protein, 33.66 ± 4.29 µmol of H_2O_2 consumed/min mg^{-1} protein respectively.

The results indicated that the level of proteins GSH, GST, CAT and SOD was restored and the level of protein restored was higher in nanoformulation LYC compared to free LYC. Thus, the results showed that the nanoformulated LYC has effective antioxidant activity compared to free LYC[24].

A similar study was done by Stojiljkovic et al[36] where they encapsulated LYC in nanoliposome and its antioxidant activity was studied in the methotrexate-induced kidney injury model. Methotrexate (MTX) was an antimetabolic drug used for the treatment of some disorders such as autoimmune disorders including osteosarcoma, breast cancer etc. which were also shown to cause oxidative tissue damage, which led to nephrotoxicity. The scientists have done liposomal encapsulation of LYC and used LYC dissolved in corn oil and compared their ability to restore the tissue damage which was caused due to the exposure of MTX in mice model. They studied 8 groups of mice treated with group1-corn oil, group 2-nanoliposomes, group 3-LYC, group 4-nanoencapsulated LYC, group 5-MTX, group 6-MTX+nanoliposome, group 7-MTX+LYC, group 8-MTX+nanoencapsulated LYC respectively.

The serum biochemical analysis showed an increased level of creatinine and urea that was observed after treatment with MTX group whereas in the case of MTX+LYC and MTX+ nanoencapsulated LYC, the levels of serum creatinine and urea were decreased. Nanoencapsulated LYC showed higher efficacy in decreasing the level of creatinine and urea compared to free LYC respectively. Tissue catalase (CAT) level was also observed to decrease after the treatment of MTX which was 24.5 ± 7.5 IU/mg whereas in control, the level of CAT was 120 ± 2.1 IU/mg and in the group treated with MTX+LYC and MTX+ nanoencapsulated LYC, it was 67.1 ± 2.1 IU/mg and 83.1 ± 3.2 IU/mg respectively. From the study, they have observed that the nanoencapsulated LYC has stronger antioxidant activity compared to free LYC[36].

In another study, scientists have formulated silver nanoparticle mediated herbal formulation containing LYC, green tea, raspberry extract and green tea extract. They have shown higher antioxidant activity with a higher absorption percentage of 93.15%[5]. Chitosan loaded with LYC has also been proven to have antioxidant activity with the help of an ascorbic acid assay. Scientists have shown that the chitosan loaded with LYC has ascorbic acid assay as an effective antioxidant activity compared to only chitosan nanoparticle[6]. Gutiérrez et al[14] formulated and studied the antioxidant activity of lycopene and double-layered doubled hydroxide nanoparticles composites. The composites are MgAl–CO_3–LYC, MgAl–Cl–Lyc and ZnAl–CO_3–LYC. Among these nanocomposites, ZnAl-CO_3-LYC showed more antioxidant activity compared to other components.

The results of *in vivo* study analysis showed that the lipoperoxides in the mitochondria increased significantly and the level of the nitrate–nitrite was decreased in the ZnAl-CO_3-LYC treated group. From this study, they have shown that the ZnAl-CO_3-LYC has superior antioxidant activity compared to other composites[14]. Ahmed et al[2] showed that the LYC loaded in polyethylene glycol (PEG) exhibited effective antioxidant activity which was confirmed by scavenging of free radicals such as DPPH and ABTS. The IC_{50} values were 0.115 ± 0.0123 µg/ml and 0.128 ± 0.0014 µg/ml for PEG-LYC nanoparticles for DPPH and ABTS assay respectively and for free LYC, it was 0.055 ± 0.0010 µg/ml and 0.057 ± 0.001 µg/ml for DPPH and ABTS assay respectively.

Anticancer activity of nano lycopene: Lycopene can inhibit the growth of various cancer cells such as lung, colon, prostate etc. via inhibition of various metabolic pathways[32]. Bano et al[3] have done PNIPAAM–PEG-based co-polymeric nanoencapsulation of commercially available LYC (C-LYC) and extracted LYC (E-LYC) and studied their anticancer activity against 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted tumor generation and skin inflammation in Swiss albino mice. They found that the nanoformulated E-LYC and C-LYC showed greater cytotoxicity activity against melanoma cell line B16 at both the concentrations (5 µg/ml, 10 µg/ml) compared to free E-LYC and C-LYC treated group at concentration of 100 µg/ml in MTT assay. Further, the apoptosis induction activity of nanoformulated E-LYC and C-LYC, free E-LYC and C-LYC showed that in the nanoformulated E-LYC (10 µg/ml) group, the percentage of cells that have undergone apoptosis was found to be higher compared to other groups.

The *in vitro* studies showed that the nanoformulated E-LYC could reduce the edema caused by TPA and the percentage of inhibition was 92.0 in 10 µg/ml and 77.8 in the 5 µg/ml group, whereas in the free LYC it was 64.0 respectively. The tumor growth after18 h of treatment with nanoformulated E-LYC (10 µg /ml) was 4.1 ± 0.91, nanoformulated E-LYC (5 µg/ml) was 5.2 ± 1.10 and for free LYC, it was 12.7 ± 1.31 respectively. They have shown that the nanoformulated LYC they extracted has enhanced anti-inflammatory and anticancer potential[3]. In another study, a group of scientists have nanoformulated the lycopene with gelatin and compared its anticancer activity against breast cancer (MCF-7) against oxaliplatin. They observed the DNA ladder formation after treatment with LYC loaded in gelatin nanoparticle at its IC_{50} concentration 0.71% (2.84 µl) by agaroses gel electrophoresis, which showed similar fragmentation as oxaliplatin treated cells at its IC_{50} concentration. A step forward, they have also performed tunnel assay and the results showed that the percentage of tunnel positive cells was 75.67%, whereas the percentage of tunnel positive cells in the oxaliplatin treated group was 65.52% respectively.

From the Annexin V FITC/PI assay, the percentage of MFC-7 cells in the late and early stage of apoptosis in LYC loaded in gelatin nanoparticle was 6.84 and 13.94% respectively whereas in the oxaliplatin treated group it was 5.65 % and 11.52% respectively. These results showed that LYC loaded in gelatin nanoparticles has enhanced ability to induce apoptosis in MFC-7 cells[29]. For the targeted relaces of LYC in colon cancer, Shejawal et al[35] nanoformulated the functioned nanotubule and from *in vitro* cytotoxicity study showed that the LYC loaded nanotube had higher cytotoxic activity against COLO320DM and HT 29 cells. From *in vivo* X-ray analysis, they have shown that the drug release was found to be at the colonic site.

Shejawal et al[35] have formulated gold, silver and iron nanoparticle using LYC (LY-GNP, LY-AgNP, LY-FeNP) extracted from tomatoes and studied their anticancer activity against COLO320DM, HT 29 and HeLa cells. The nanoformulations' cytotoxicity was studied using MTT, SBR and Trypan blue assay. From the MTT assay, it was found that LY-AgNP had higher inhibition percentage (41.41 ± 0.4124 %) against COLO320DM and 40.9 ± 0.6908 % against HeLa cells. LY-GNP showed higher inhibitory activity (41.47 ± 0.4469 %) against HT29. From the SBR assay, the percentage of inhibition of cells was found to be higher in LY-AgNP for COLO320DM cells (82.68 ± 1.1798%) whereas LY-GNP showed killing in HT29 cells

(91.21 ± 0.2372%) and in HeLa cells (87.98 ± 0.5878%) which was found to be higher compared to other groups. They also did trypan blue staining and the percentage of cell inhibition was found to be more in LY-GNP treated cells in COLO320DM (83.45 ± 0.4694%) and HT29 (80.72 ± 0.8134%).

In HeLa cells, the inhibitory percentage was higher in LY-AgNP treated cells which were 65.47 ± 0.4766 %. These experiments have shown that all nanoformulation have superior anticancer activity compared to free LYC and that the LY-AgNP and LY-GNP have higher anticancer activity when compared to LY-FeNP[34]. Vasconcelos et al[38] formulated a self-emulsifying drug delivery system (SEDDS) loaded with LYC (SE-LYC) and studied the *in vivo* toxicity on mice and cytotoxicity on human peripheral blood mononuclear cells (PBMC) and prostate carcinoma cells (DU-145). From this study, they have observed that the mice orally treated with the SE-LYC 10 mg/kg for 28 days did not show any significant changes and thus the SE-LYC formulation was confirmed to be nontoxic. They have also found that the LYC was delivered in the kidney (0.1118±0.0239 µg/g), prostate (0.0320±0.0070 µg/g) and liver (0.1829±0.0927 µg/g) after 28 days of treatment.

In the cytotoxicity study on prostate cancer cells, the percentage of cell viability reduction at lower concentration (3.125 µg/ml) was 19.33 ± 2.36% after 6 h of treatment for free LYC and for SE-LYC, it was found to be 44.65 ± 6.90 % with 3.125 µg/ml concentration of the sample. In PBMC the cytotoxicity of SE-LYC was 6.36±3.43 % at a concentration 25 µg/ml, whereas for 0.75 µg/ml of free LYC, the percentage of cytotoxicity was 13.43±1.13%, which was higher compared to SE-LYC. This showed that the SE-LYC has less cytotoxicity towards PBMC than free LYC. They also observed that the SE-LYC nanoformulation had higher cytotoxic activity against DU-145 cells and exhibited enhanced anticancer activity that was target specific[38].

Mennati et al[23] formulated a lipid hybrid nanocarrier that carries LYC with methoxy polyethylene glycol-polycaprolactone (mPEG-PCL) and dimethyldioctadecylammonium bromide (DDAB) to enhance the cellular uptake of LYC and they studied the anticancer effect of this nanoparticle on breast cancer cell line. The cytotoxicity studies indicated that the IC_{50} value of the free LYC and nanoformulated LYC was 88.25 ± 0.16 µM and 138.9 ± 0.19 µM respectively.

The *in vivo* study was done on female albino mice and it was found that the formulated nanoparticle does not have any toxic effect on the kidney, spleen, liver and heart and their morphology was found to be similar to the control. They also identified that in the nanoformulated LYC group, the presence of insulin-linked growth factor-1 receptor gene level was lower compared to the cells treated with control and free LYC in MCF-7 cells. The percentage of cells undergoing apoptosis was 62.5% in nanoformulated LYC, which was higher compared to control and free LYC, which showed an apoptotic percentage of 29.3% and 58.6% respectively. The percentage of the cell population was either increased or decreased (indicated by up arrow and down arrow) at different stages of cell growth for nanoformulated LYC and LYC, compared to control. The cell percentage at G1 phase was 11.54±0.9↓ and 10.37±1.2↑, S phase 15.08±0.9↑ and 2.57±1.2↓ and in G2/M phase 4.54±0.9↓ and 0.49±1.2 ↓ for nanoformulated LYC and LYC respectively. The results showed that there was a significant change compared to control in the cell cycle distribution of MCF-7 cells.

This study observed that the nanoformulated LYC can effectively inhibit the growth of MCF-7 cancer cells via inducing apoptosis and downregulating the IGF-1R gene and did not have any toxic effect on *in vivo* animal model[23]. A similar study was done by the same group of scientists where they nanoformulated LYC with the same particle mPEG-PCL and DDAB, but along with this, they also tagged siRNA specific for IGF-1 receptor and found that this dual delivery of LYC along with siRNA induces apoptosis and cell death in MCF-7 cell line effectively[22]. Jain et al[18] nanoformulated LYC with whey protein isolate nanoparticles and studied its anticancer activity against MCF-7 cancer cell lines. They also studied the nanoformulated drug delivery capacity *in vivo* model induced with breast cancer and observed that the drug was delivered at the target site after oral administration.

The cytotoxicity studies showed that the nanoformulated LYC could inhibit the growth of MCF-7cells based on dose and time-dependent manner. The cellular uptake of the drug was found to be higher after 5 h of treatment and was 64.2±4.1% for nanoformulated LYC and 33.07±2.8% for free LYC. The presence of drug at the tumor site was higher at 8 h after administration which gradually decreased at 24 h. From this study, they have shown that the nanoformulated LYC had higher cellular availability and tumor reduction capacity compared to free LYC[18].

Ghazi et al[10] studied the synergistic effect of two components, LYC and propolis, which were nanoformulated with phytosome individually and in their combination (LY-PH, PR-PH and LY/PR-PH). They studied the cytotoxicity of nanoformulations in prostatic hyperplasia cells *in vitro*. From the observation, the IC_{50} of LY-PH was found to be 89.74 µg/ml, PR-PH was 58.46 µg/ml and LY/PR-PH was 47.86 µg/ml respectively. These data indicated that the combination of LYC and PR nanoformulation had more efficacy in the inhibition of cell growth compared to the individual component nanoformulation.

Ahmed et al[2] studied the anticancer activity of nanoformulated LYC with PEG (LYC-PEG). They studied the antiproliferative effect of LYC-PEG on five different types of cancer cell lines which are HepG-2, MCF-7, HCT-116, MCF12F and BJ-1. The percentage of cytotoxicity in

each cell line was 54.03±0.4% (MCF-7), 6.65±0.03% (MCF12F), 69.06±0.67% (HepG2), 66.7±0.77% (HCT-116) and 1.38±0.05% (BJ-1) for LYC-PEG at a concentration of 100 µg/ml and for free LYC, the viability was 69.5 ± 1.4% (MCF-7), 8.6 ±0.40 % (MCF12F), 85.5 ± 0.87% (HepG2), 58.3 ± 0.74% (HCT-116) and 1.4 ± 0.023% (BJ-1) respectively. From this observation, they have shown that the LYC-PEG had enhanced anticancer activity against HepG-2, MCF-7 and HCT-116 compared to free LYC[2].

Other applications activities of nanoformulated Lycopene: LYC has various biomedical applications such as anticancer, antioxidant, anti-inflammatory, antimicrobial activity etc. There are various nanoformulations that can enhance the biomedical activity of LYC[4]. Murthykumar et al[25] have nanoformulated LYC with silver nanoparticle (LYC-AgNP) and studied antimicrobial activity against *Staphylococcus aureus* and *Streptococcus mutans.* The zone of inhibition (ZOI) was found to be higher when they were incubated with 50 µg/ml against *Staphylococcus aureus* (ZOI=15 mm) and at 100 µg/ml against *Streptococcus mutants*, the ZOI was 18 mm. It was proven that the LYC-AgNP could inhibit the growth of microbes in a dose-dependent manner.

Ahmed et al[2] nanoformulated LYC with PEG and studied its antibacterial and antifungal activities against various microbes such as Gram-negative bacteria like *Pseudomonas aeruginosa* NRRL B-272, *Escherichia coli* O157-H7 ATCC 51659 and *Salmonella typhi* ATCC 15566; and also tested against Gram-positive bacteria such as *Staphylococcus aureus* ATCC 13565 and *Bacillus cereus* EMCC 1080. The minimum inhibitory concentration (MIC) for LYC-PEG was found to be 0.167 and 0.667 mg/ml for *P. aeruginosa* and *S. aureus,* respectively and for free LYC, the MIC was 0.092 and 0.50 mg/ml for *P. aeruginosa* and *S. aureus* respectively. The ZOI for LYC-PEG treatment at 33.3 mg/ml was monitored for each bacteria and was 12.3±0.58 mm for *B. cereus*, 10±0.58 mm for *S. Aureus*, 8.3±0.57 mm for *E.coli*, 8.6±0.53mm for *S.typhi* and 8.3±0.58 for *P. aeruginosa* respectively.

They also studied the antifungal activity of LYC/PEG and the MIC was maximum for *A. niger* and *P.verrucosum*, which was approximately 0.2 and 0.8 mg/ ml for *A. niger* and *P.verrucosum*, respectively; whereas for free LYC it was found to be 0.208 and 1.33 mg/ ml for *A. niger* and *P.verrucosum*, respectively. The ZOI for LYC/PEG (33.3 mg/ml) was found to be 14.1±2.84 mm for *A.flavus*, 13.3±2.52mm for *A.parasiticus*, 11.6±0.76 mm for *A.ochracious*, 13.8±1.15 mm for *F.proliferitum* and 12.3±3.1 mm for *P.verrucosum* respectively. From this study, they have shown that the nanoformulated LYC has effective antimicrobial activity against different bacteria and fungus[2]. YC has also been shown to have anti-inflammatory activity when nanoformulated with chitosan, which was confirmed by diclofenac sodium assay in a dose-dependent manner[21].

Pirsa et al[27] formulated biodegradable nanocomposite biofilm for food packaging for the storage of margarine. The nanocomposite consists of polylactic acid (PLA), titanium dioxide (TiO_2) and lycopene (Lyc) (PLA/TiO_2/Lyc) and PLA/Lyc. The mechanical property of the biofilim was found to improve after the addition of PLA and TiO_2. The PLA/TiO_2/Lyc nanocomposite was found to be stable at refrigerator storage temperature after 60 days whereas a color change was observed in the PLA/Lyc nanocomposite.

The oxidative and color properties of margarine were improved in both the films PLA/TiO_2/Lyc and PLA/Lyc. This observation shows that PLA/TiO_2/Lyc can act as a smart and active biofilm for food packaging[27].

Conclusion

The nano LYC has shown a prominent anticancer and antioxidant activity which was higher compared to free LYC. Nanoformulation of LYC helped to maintain the stability, bioavailability etc. which improved the drug availability and drug circulation, exerting higher killing of cancer cells and tumor reduction in the animal model and enhancing the antioxidant activity via effective scavenging of free radicals. The role of nanoformulated LYC is necessary to be explored for their various biomedical activities.

References

1. Agraharam G., Girigoswami A. and Girigoswami K., Nanoencapsulated Myricetin to Improve Antioxidant Activity and Bioavailability: A Study on Zebrafish Embryos, *Chemistry*, https://doi.org/10.3390/chemistry4010001, **4**, 1-17 **(2022)**

2. Ahmed H.A., Salama Z.A., Salem S.H., Aly H.F., Nassrallah A., Elella A.F. and Enein A.A.M., Lyopene Nanoparticles Ameliorate the Antioxidants, Antimicrobial and Anticancer Potencies of Tomato Pomace, *Egyptian Journal of Chemistry*, https://doi.org/10.21608/EJCHEM.2021.71766.3583, **64(7)**, 3739-3749 **(2021)**

3. Bano S., Ahmed F., Khan F., Chaudhary S.C. and Samim M., Targeted delivery of thermoresponsive polymeric nanoparticle-encapsulated lycopene: in vitro anticancer activity and chemopreventive effect on murine skin inflammation and tumorigenesis, *RSC Advances*, https://doi.org/10.1039/c9ra10686c, **10(28)**, 16637-16649 **(2020)**

4. Caseiro M., Ascenso A., Costa A., Flynn C.J., Johnson M. and Simões S., Lycopene in human health, *LWT*, https://doi.org/10.1016/j.lwt.2020.109323, **127**, 109323 **(2021)**

5. Chaithanya M.V., Maheswari T.U. and Rajeshkumar S., Anti-inflammatory and antioxidant activity of lycopene, raspberry, green tea herbal formulation mediated silver nanoparticle, *Journal of Indian Academy of Oral Medicine and Radiology*, **33(4)**, 397 **(2021)**

6. Dave P.H., Gajendran P.L., Arjunkumar R. and Rajeshkumar S., *In vitro* antioxidant activity of chitosan nanoparticles and its incorporated lycopene, *Plant Cell Biotechnology and Molecular Biology*, **21(27-28)**, 45-53 **(2020)**

7. De S., Gopikrishna A., Keerthana V., Girigoswami A. and Girigoswami K., An Overview of Nanoformulated Nutraceuticals and their Therapeutic Approaches, *Current Nutrition & Food Science*, https://doi.org/10.2174/1573401316999200901120458, **17(4)**, 392-407 **(2021)**

8. Dharshni T., Thendral V., Murugesan R., Girigoswami A. and Koyeli Girigoswami K., Dual Role of Nano Ceria- as an Antioxidant and as a Prooxidant, *Chettinad Health City Medical Journal*, https://dx.doi.org/10.36503/chcmj9(1)-11, **9(1)**, 59 – 65 **(2020)**

9. Fariana Nur Santi, Yuspian Nur, Agung Rahmadani, Herman and Hadi Kuncoro, Synthesis and Bioactivity of New Pyrazoline Derivative: N-carbamide-3-(2,4-dichlorophenyl)-5-(4-hydroxy-3-methoxyphenyl)pyrazoline, *Res. J. Chem. Environ.*, **23(12)**, 55-59 **(2019)**

10. Ghazi A.M. and Bayati A.M.A., Anti-proliferative of the phytosome propolis, phytosome lycopene and synergistic effect on the benign prostatic hyperplasia cells in-vitro, *Plant Archives*, **20(2)**, 6579-6589 **(2020)**

11. Ghosh R., Girigoswami K. and Dipanjan G., Suppression of apoptosis leads to cisplatin resistance in V79 cells subjected to chronic oxidative stress, *Indian Journal of Biochemistry & Biophysics*, **49(5)**, 363–370 **(2012)**

12. Girigoswami A., Ghosh M.M., Pallavi P., Seenuvasan R. and Girigoswami K., Nanotechnology in Detection of Food Toxins – Focus on the Dairy Products, Proceedings internationals, https://dx.doi.org/10.33263/Proceedings31.025025, **3(1)**, 25 **(2021)**

13. Girigoswami K. and Girigoswami A., A Review on the Role of Nanosensors in Detecting Cellular miRNA Expression in Colorectal Cancer, *Endocr Metab Immune Disord Drug Targets*, https://dx.doi.org/10.2174/1871530320666200515115723, **21(1)**, 12-26 **(2021)**

14. Gutiérrez G.D.K., Moisés P.F.P., Bezerra S.F., Matos A.D.N., Rojas G.N.A., Quijada A.J. and Carbajal Arízaga G.G., Hydrophilic lycopene-coated layered double hydroxide nanoparticles to enhance the antioxidant activity and the oxidative stress evaluation, *Applied Nanoscience*, https://doi.org/10.1007/s13204-021-02205-8, **11(11)**, 2747-2758 **(2021)**

15. Haribabu V., Girigoswami K., Sharmiladevi P. and Girigoswami A., Water–Nanomaterial Interaction to Escalate Twin-Mode Magnetic Resonance Imaging, *ACS Biomaterials Science & Engineering*, https://dx.doi.org10.1021/acsbiomaterials.0c00409, **6(8)**, 4377-4389 **(2020)**

16. Hayes J.D., Dinkova-Kostova A.T. and Tew K.D., Oxidative stress in cancer, *Cancer Cell*, **38(2)**, 167-197 **(2020)**

17. Imran M., Ghorat F., Ul-Haq I., Ur-Rehman H., Aslam F., Heydari M., Shariati M.A., Okuskhanova E., Yessimbekov Z., Thiruvengadam M., Hashempur M.H. and Rebezov M., Lycopene as a Natural Antioxidant Used to Prevent Human Health Disorders, *Antioxidants (Basel)*, **9(8)**, 706 **(2020)**

18. Jain A., Sharma G., Ghoshal G., Kesharwani P., Singh B., Shivhare U.S. and Katare O.P., Lycopene loaded whey protein isolate nanoparticles: An innovative endeavor for enhanced bioavailability of lycopene and anticancer activity, *International Journal of Pharmaceutics*, https://doi.org/10.1016/j.ijpharm.2018.04.061, **546(1-2)**, 97-105 **(2018)**

19. Kavya J., Amsaveni G., Nagalakshmi M., Girigoswami K., Murugesan R. and Girigoswami A., Silver Nanoparticles Induced Lowering of BCl2/Bax Causes Dalton's Lymphoma Tumour Cell Death in Mice, *Journal of Bionanoscience*, **7(3)**, 276-281 **(2013)**

20. Kumar V.N.P., Elango P., Asmathulla S. and Kavimani S., A Systematic Review on Lycopene and Its Beneficial Effects, *Biomedical & Pharmacology Journal*, https://dx.doi.org/10.13005/bpj/1335, **10(4)**, 2113-2120 **(2017)**

21. Kumaran H., Gajendran P.L., Arjunkumar R. and Rajesh S., Anti-inflammatory activity of lycopene and its based chitosan nanoformulation-an in vitro study, *Plant Cell Biotechnology and Molecular Biology*, https://www.ikppress.org/index.php/PCBMB/article/view/5559, **21(51-52)**, 91-100 **(2020)**

22. Mennati A., Rostamizadeh K., Manjili H.K., Fathi M. and Danafar H., Co-delivery of siRNA and lycopene encapsulated hybrid lipid nanoparticles for dual silencing of insulin-like growth factor 1 receptor in MCF-7 breast cancer cell line, *International Journal of Biological Macromolecules*, https://doi.org/10.1016/j.ijbiomac.2021.12.197, **200**, 335-349 **(2022)**

23. Mennati A., Rostamizadeh K., Manjili H.K., Mousavi M.A., Zhiani M., Sabouri I., Attari E., Fathi M. and Danafar H., Synthesis of methoxy poly (ethylene glycol)-poly (ε-caprolactone) diblock copolymers hybridized with DDAB cationic lipid as the efficient nanocarriers for in vitro delivery of lycopene into MCF-7 breast cancer cells, *Journal of Drug Delivery Science and Technology*, https://doi.org/10.1016/j.jddst.2021.102806, **66**, 102806 **(2021)**

24. Mishra S.B. and Kumari N., Engineering of Crystalline Nano-Suspension of Lycopene for Potential Management of Oxidative Stress–Linked Diabetes in Experimental Animals, *Bio Nano Science*, https://doi.org/10.1007/s12668-021-00843-4, **11(2)**, 345-54 **(2021)**

25. Murthykumar K., Malaiappan S. and Rajeshkumar, Antioxidant and antibacterial effect of lycopene mediated silver nanoparticle against staphylococcus aureus and streptococcus mutans-an *in vitro* study, *Plant Cell Biotechnology and Molecular Biology*, **21(35-35)**, 90-8 **(2021)**

26. Owoyokun T., Berumen C.M., Luévanos A.M., Cantú L. and Ceniceros A.C., Cellulose Nanocrystals: Obtaining and Sources of a Promising Bionanomaterial for Advanced Application, *Biointerface Research in Applied Chemistry*, https://dx.doi.org/10.33263/BRIAC114.1179711816, **11(4)**, 11797 – 11816 **(2021)**

27. Pirsa S. and Asadi S., Innovative smart and biodegradable packaging for margarine based on a nano composite polylactic acid/lycopene film, *Food Additives & Contaminants*, Part A, https://doi.org/10.1080/19440049.2021.1891299, **38(5)**, 856-869 **(2021)**

28. Pizzino G., Irrera N., Cucinotta M., Pallio G., Mannino F., Arcoraci V., Squadrito F., Altavilla D. and Bitto A., Oxidative Stress: Harms and Benefits for Human Health, *Oxidative Medicine and Cellular Longevity*, https://doi.org/10.1155/2017/8416763, **2017**, 8416763 **(2017)**

29. Preetha K.M. and Devasena T., Lycopene loaded gelatin nanoparticles induces internucleosmal DNA fragmentation and apoptosis in human breast adenocarcinoma cells, *Materials Research Express*, https://doi.org/10.1088/2053-1591/aac7b3, **5(6)**, 065016 **(2018)**

30. Przybylska S., Lycopene–a bioactive carotenoid offering multiple health benefits: a review, *International Journal of Food Science & Technology*, https://doi.org/10.1111/ijfs.14260, **55(1)**, 11-32 **(2020)**

31. PubChem [Internet], Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information, PubChem Compound Summary for CID 446925, Lycopene, https://pubchem.ncbi.nlm.nih.gov/compound/Lycopene **(2004)**

32. Sahin K., Orhan C., Sahin N. and Kucuk O., Anticancer properties of lycopene, *Bioactive Molecules in Food*, https://doi.org/10.1007/978-3-319-54528-8_88-1, **2019**, 935-969 **(2019)**

33. Sharmiladevi P., Breghatha M., Dhanavardhini K., Priya R., Girigoswami K. and Girigoswami A., Efficient Wormlike Micelles for the Controlled Delivery of Anticancer Drugs, *Nanoscience & Nanotechnology-Asia*, https://dx.doi.org/10.2174/2210681210999200728115601, **11(3)**, 350-356 **(2021)**

34. Shejawal K.P., Randive D.S., Bhinge S.D., Bhutkar M.A., Todkar S.S., Mulla A.S. and Jadhav N.R., Green synthesis of silver, iron and gold nanoparticles of lycopene extracted from tomato: their characterization and cytotoxicity against COLO320DM, HT29 and Hella cell, *Journal of Materials Science: Materials in Medicine*, https://doi.org/10.1007/s10856-021-06489-8, **32(2)**, 1-2 **(2021)**

35. Shejawal K.P., Randive D.S., Bhinge S.D., Bhutkar M.A., Wadkar G.H., Todkar S.S. and Mohite S.K., Functionalized carbon nanotube for colon-targeted delivery of isolated lycopene in colorectal cancer: *In vitro* cytotoxicity and *in vivo* roentgenographic study, *Journal of Materials Research*, **36**, 4894–4907 **(2021)**

36. Stojiljkovic N., Ilic S., Jakovljevic V., Stojanovic N., Stojnev S., Kocic H., Stojanovic M. and Kocic G., The encapsulation of lycopene in nanoliposomes enhances its protective potential in methotrexate-induced kidney injury model, *Oxidative Medicine and Cellular Longevity*, https://doi.org/10.1155/2018/2627917, **(2018)**

37. Suo S., Lai Y., Li M., Song Q., Cai J., Zhao J., Yang Q., Ung C.O. and Hu H., Phytochemicals, pharmacology, clinical application, patents and products of Amomi fructus, *Food and Chemical Toxicology*, https://doi.org/10.1016/j.fct.2018.05.051, **119**, 31-36 **(2018)**

38. Vasconcelos A.G., Barros A.L., Cabral W.F., Moreira D.C., Silva D.I.G., Carvalho S.A.É., de Almeida M.P., Albuquerque L.F., Santos D.R.C., Brito S.A.K. and Saldanha-Araújo S.F., Promising self-emulsifying drug delivery system loaded with lycopene from red guava (Psidium guajava L.): *in vivo* toxicity, biodistribution and cytotoxicity on DU-145 prostate cancer cells, *Cancer Nanotechnology*, https://doi.org/10.1186/s12645-021-00103-w, **12(1)**, 1-29 **(2021)**

39. Woldeamanuel K.M., Kurra F.A. and Roba Y.T., A review on nanotechnology and its application in modern veterinary science, *International Journal of Nanomaterials, Nanotechnology and Nanomedicine*, https://dx.doi.org/10.17352/2455-3492.000041, **7(1)**, 26-31 **(2021)**.

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