



## Pharmacological Effects of Lycopene - A Review

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### ABSTRACT

Carotenoids are pigments that are lipophilic in nature. Lycopene is an important dietary carotenoid that has been seen to be effective in managing and treating various medical conditions. It has aliphatic properties. It can be isolated from watermelons, tomatoes, and papayas. All the studies were examined separately according to need, like, dose determination, comparison with other similar products, their concentration in body fluid and also their effectiveness at different sites and types of comorbidities. It can prevent inflammatory and oxidative properties. Lycopene has pharmacological effects in diseases related to the central nervous system like Epilepsy, Alzheimer's disease, Parkinson's disease along with this it also exhibits Cardioprotective and anti-microbial properties. It is also noteworthy to mention that antioxidants help in protecting and preventing the condition of atherosclerosis.

**Keywords:** Antibiotics, Anti-microbial, Neuroprotective, Cardioprotective, Lycopene, Lung infection, Chronic Prostatitis.

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### INTRODUCTION

The drug-resistant strains of bacteria are emerging and the scientific communities have prioritized their searching for an alternate mode of treatment due to the phenomenon of 'antibiotic- resistance'. In this light enormous work has been done on the discovery and development of naturally occurring agents to treat and possibly reduce the development of severe medical complications. Many studies have been conducted to exploit the use of lycopene in the treatment of various medical conditions. Lycopene is a natural non-provitamin bioactive, aliphatic hydrocarbon carotenoid extracted from several fruits and vegetables like tomatoes, papayas, watermelons, etc, that is responsible for the red to pink colour in various fruits and vegetables<sup>1</sup>.

Lycopene has anti-proliferative, anti-inflammatory, and strong antioxidant properties. It also shows a protective role against a range of diseases in both in vivo and in vitro studies. It has been proven effective in the treatment of various disorders including non-alcoholic fatty liver disease, heart malignant tumour, prostate cancer, type II diabetes, neurodegenerative and psychiatric disorders.<sup>1,2</sup> Its effectiveness can also be seen in the treatment of certain other diseases like asthma, chronic obstructive lung disease (COPD) and emphysema, acute lung injury (ALI), pulmonary fibrosis.<sup>1,3</sup> It also has cancer-preventive

properties against several types of cancer, including lung, colon, and prostate cancer. Higher consumption of dietary lycopene as a major natural antioxidant and carotenoid in tomatoes and tomato products can significantly decrease the risk of lung cancer in smokers. Serum lycopene has been positively allied with an improvement of lung function in COPD patients.<sup>3</sup> Lycopene acts as a natural bioactive antioxidant carotenoid on oxidative stress and pulmonary function tests (PET) in patients with COPD.<sup>3</sup>

Apart from this, many experiments have been carried out to evaluate the antibacterial activity of lycopene compared to standard antibiotics. Lycopene content in methanolic extract of *Nasturtium officinale* was found effective against *Escherichia coli*, *Klebsiella pneumonia*, *Enterococcus faecalis*, and *Bacillus cereus*.<sup>4</sup> More antibacterial activity of lycopene mediated silver nanoparticles was noted against *S. aureus* at 50 µg/ml compared to the standard antibiotic (Amoxicillin 12.5mg/ml) whereas almost similar activity was found between *S. mutans* and Amoxicillin.<sup>5</sup> The antimicrobial effect of lycopene extract against *S. aureus*, *S. pyogenes*, *P. aeruginosa* & *E. coli* was determined using the well diffusion technique. A parallel group-quasi control trial was carried out to understand the effect of lycopene in the eradication of antibiotic-resistant *Helicobacter pylori*.<sup>6</sup> Similarly, the antibacterial activity of lycopene was estimated against five drug-resistant bacterial pathogens namely *Staphylococcus aureus*, *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* isolated from the wound.<sup>7,8</sup> A synergistic effect was noticed when the Chronic Bacterial Prostatitis rat model had been developed and treated using lycopene and ciprofloxacin together.<sup>9</sup> This finding depicts that combination therapy of fluoroquinolone and lycopene can improve the treatment efficacy of Chronic Bacterial



Prostatitis. As the attention has been shifted from antibiotic therapy to phytotherapy, more appropriate studies should be carried out to elucidate the exact mechanism of action of lycopene.<sup>9</sup>

## METHODS

The study was conducted using four databases: Google Scholars, SAGE, DOAJ, and PubMed. The selection of papers was done based on keywords and themes relevant to this review. Further, the published papers from these databases were arranged in systematic order with respect to the year of publication.

## RESULTS AND DISCUSSION

### Antibiotics in treatment of diseases

Out of four groups studied for the effect of Cefpodoxime, A, B, C and, D, groups A and B showed much fluctuation in pH and showed more gastrointestinal symptoms.<sup>10</sup> Inflammation occurred in the large intestine by administration of *C. difficile* by the production of enterotoxin and cytotoxin. The efficacy of cefpodoxime is less as compared to cefixime. Drugs were affected against gram-positive bacteria only. Cefpodoxime is much more effective than penicillin and treats skin infections. A cephalosporin is an alternative approach in PAOM treatment.<sup>10</sup> By producing cephalosporins-coated OMVs, the human GI tract can prevent *Salmonella* and other commensal microbes.<sup>10</sup> A very low amount of cefpodoxime and amoxicillin was present in saliva. The concentration of amoxicillin was also absent on faeces. By administration of amoxicillin, there was a decline in the concentration of streptococci and staphylococci. However, it had no side effects. At low gastric pH and in the fed stage, cefpodoxime proxetil shows good absorption.<sup>10</sup> As compared to Amoxicillin, cefpodoxime is more competitive for gram-negative bacteria.<sup>10</sup> In the case of irradiated animals, antimicrobial agents which are against strict anaerobic bacteria are deleterious and these agents which were against lactose fermenting species proved to be helpful. In the saliva samples, levofloxacin and ofloxacin were absent on days 0, 9, 11, 14, 21.<sup>10</sup> Cefixime has therapeutic value in treating typhoid fever by inhibiting the growth of bacteria in cells. This drug is effective in both cases in vivo and in vitro. To sort cells or to isolate stem cells, an approach of FACS was used. The higher MIC value in *E. coli* and *S. aureus* showed their resistance towards cefixime. Cefixime can effectively treat UTIs as it shows a wide spectrum of antibacterial activity in the case of both gram-positive and gram-negative bacteria.<sup>10</sup> However, the administration of cefixime showed some minor side effects like gastritis, rashes, nausea and drowsiness. On the increase of temperature to 600°C, the weight of the cefixime sample decreases.<sup>10</sup> Prepared nanoparticle samples showed effective results against bacterial strains rather than a raw drug. Upon continuous intake of cefixime, there is an increase in Bacteroidetes and a decrease in Firmicutes and also there is an upsurge in the Bacteroidetes/Firmicutes ratio by 32%.<sup>10</sup>

In a study to know the synergic impact of ohmic heating and UV-C irradiation to inactivate strains of *Escherichia coli* O157:H7, *Salmonella Typhimurium*, and *Listeria monocytogenes*. *E.coli* O157:H7, *S. Typhimurium*, and *L. monocytogenes* were inactivated by treatment of the combination of UV-C irradiation and ohmic heating.<sup>11</sup> The combination of OH and UV showed maximum damage of cell membrane and lipid peroxidation as observed by PI uptake and DPPH test, respectively. <sup>11</sup> *L. monocytogenes* show maximum PI value because the peptidoglycan layer is thick in Gram-positive microorganisms and they also do not have an outer membrane. The greatest variance was shown in BPW.<sup>11</sup> The most effective result was observed in thermal treatment rather than non thermal treatment. By *E.coli*, *S. Typhimurium*, and *L. monocytogenes*, this was taken to reach 5-log reduction were 4.54, 4.06, and 3.96 S, respectively for OH and OH+UV, it is 4.16, 3.85 and 3.76 for *E. coli* O157:H7, *S. Typhimurium* and *L. monocytogenes* respectively.<sup>11</sup>

In a study on the Strain of Enteric Bacteria Present in Retailed Tomato Found in Southwest Nigeria. On day 5, at 25°C, the tomato showed rottenness, fungal growth and early spoilage.<sup>12</sup> At 4°C(Refrigerated), tomatoes remain fresh throughout the experiment. After 14 days, broken cell walls, yellow fluid production, and heavy fungal growth were observed at 25°C.<sup>12</sup> The bacterial count at ambient temperature(25°C) was 4-7.18 Log CFU /g and the count was more at refrigerated temperature.<sup>12</sup> At ambient temperature, the bacteria count showed a steady rise on days 8-10. *Aeromonas* spp.(2.6%), *Citrobacter* spp.(25.5%), *Bacillus* spp.(18.2%), *proteus* spp.(7.2%), *Enterobacter* spp.(10.8%) and *Klebsiella* spp.(35.7%) were identified bacteria.<sup>12</sup> The bacterial strain of tomato fruits shows antibiotic resistance for beta-lactamase antibiotics like ceftazidime, cefuroxime, cefixime, ciprofloxacin, and amoxicillin-clavulanic acid. 5-25 ng was DNA yield which was extracted and purified with an absorbance ratio of 1.60-1.80. *Klebsiella aerigenes* B18 and *Citrobacter freundii* B27 were resistant enteric bacteria strains.<sup>12</sup>

### Phytochemicals in the treatment of diseases

As the wound infections caused by antibiotic-resistant bacteria became a serious public health concern, phytochemicals catch huge attention to explore their antimicrobial activity against drug-resistant clinical pathogens.

A proteolytic enzyme known as Papain has wide use in industries. It is a polygamous species. It can be staminate, bisexual or, pistillate. Leaves are 30-70 cm spirally arranged on petioles with a life span of 4-6 months.<sup>13</sup> Flowers are of 6 types in the papaya plant. It has yellow-orange ovoid melon-like fruit. 16% weight of fruit consists of seeds made up of sarcotesta and endosperm. Several medicinal and nutritional properties are there in seed extract.<sup>13</sup> The stem of papaya is cylindrical and has a diameter of 10-30 cm. The plant has many active chemical compounds. Its leaves have saponin, flavonoids, alkaloids, tannin, and glycosides. Ca, Fe, Mg, K, Mn are present in



shoots. Beta carotene and cryptoxanthin are present in fruits.<sup>13</sup> Severe health effects are caused by free radicals and these radicals can be eliminated by using antioxidants. A good antioxidant property is shown by the *C. papaya* male flower.<sup>13</sup> The disc diffusion method was used to check fresh and dried leaves extracts' antimicrobial activity. It was observed that organic extracts were more effective than aqueous extracts. Antimicrobial activity was shown against *Pseudomonas aeruginosa* by papaya leaf.<sup>13</sup> The antidiarrheal activity was shown by raw *C. papaya* chloroform extract (25 mg/ml) and by ripe *C. papaya* acetone extract (25-0.39 mg/ml).<sup>13</sup> Papaya can also cure skin diseases and wounds. *C. papaya* also has anti-cancer properties as it has papain which is used in cancer treatment. It also shows antimalarial activity.<sup>13</sup> Papaya has flavonoids, saponins, alkaloids, and tannins. All these are secondary metabolites that can decrease inflammation.<sup>13</sup>

In an attempt to prevent bacterial leaf spot disease in *Carica papaya* (Papaya) by a therapeutic approach using soil bacteria and therapeutic plants.<sup>14</sup> After incubation for 16 hours at 37°C, bacterial liquid culture was obtained and PCR was used to detect the pathogen.<sup>14</sup> Soil bacteria isolates were prepared from 4 different places. The 1st isolate showed a yellow colony while creamy white colonies were shown by 2nd, 3rd and 4th isolates. The maximum zone of inhibition at 40 microliter/disc concentration by isolates 1 and 2 was shown at 12±0.2 mm and by 3 and 4 at 11±0.2mm and 9±0.4mm respectively.<sup>14</sup> Methanol extract of *Lantana camara* shows the highest zone of inhibition at 100 microgram/ml (17mm) and 60 micrograms/ml highest zone of inhibition was shown by ethanol extract (13.5mm).<sup>14</sup> *Tagetes erecta* petroleum ether extract show maximum zone of inhibition at 60 microgram/ml (11mm).<sup>14</sup> In the case of antibiotics, the maximum zone of inhibition was shown against erythromycin (24mm) and lowest against nalidixic acid and carbenicillin (8mm) for the causal pathogen of bacterial leaf spot.<sup>14</sup>

Apart from these, Lycopene has also been heavily studied and researched to study its pharmacological effects.

#### Antimicrobial effects of Lycopene.

One of the studies conducted by Malaiappan et al. (2020) depicts the antibacterial activity of lycopene mediated silver nanoparticles against two Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus mutans*), which are mainly involved as causative agents of Periodontitis and dental caries disease.<sup>5</sup> A commercially available lycopene capsule (Healthvit) was used to synthesize lycopene-mediated silver nanoparticles. It was then tested for antibacterial activity against common oral pathogens like *S. mutans* and *S. aureus* using the agar well diffusion method.<sup>5</sup> Four wells with a diameter of 6 mm have been made on each culture inoculated Petri plate containing Muller Hinton Agar medium. 20 µg/ml of different concentrations of lycopene mediated silver nanoparticles (25 µg/ml, 50 µg/ml & 100 µg/ml) were poured in each well. Amoxicillin (AMOXIL) 12.5 mg/ml antibiotic has been

used as a positive control to compare the sensitivity test of each pathogenic bacterium against lycopene-mediated silver nanoparticles.<sup>5</sup> Increased clear halo zone formation was observed at the increased concentration of lycopene-mediated silver nanoparticles.<sup>5</sup> Larger and smaller halo formation against *S. aureus* was seen at a concentration of 50 µg/ml and 25 µg/ml respectively. Whereas larger inhibition halo was noted against *S. mutans* at a concentration of 100 µg/ml.<sup>5</sup> High inhibition halo was noted against *S. aureus* at 50 µg/ml compared to amoxicillin whereas, against *S. mutans*, amoxicillin formed a little larger halo.<sup>5</sup>

Hraishawi et al. (2020) suggest various methods for lycopene extraction followed by an evaluation of its antibacterial activity.<sup>7</sup> Extracted lycopene was further diluted (25, 50, 75, and 100 mg/ml) and used to examine the antimicrobial activity by well diffusion technique against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, and *Escherichia coli*. 100 µl of lycopene extract from four concentrations (25, 50, 75, and 100 mg/ml of Dimethyl Sulfoxide (DMSO) was pipetted into the wells in the Muller Hinton agar Petri plates.<sup>7</sup> The largest zone of inhibition was noted against *P. aeruginosa* in 100mg/10ml DMSO.<sup>7</sup> Antibacterial action was proportionally associated with the increasing concentration of lycopene extract.<sup>7</sup> Ezeanya-Bakpa et al. (2021) conducted a study to estimate the antibacterial activity of lycopene against drug-resistant bacteria (*Staphylococcus aureus*, *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia*) isolated from the wound.<sup>8</sup> Antibiotic susceptibility profiles of the isolated bacteria were confirmed by disc diffusion method using Augmentin (10 µg), Gentamicin (30 µg), Ciprofloxacin (30 µg), and Streptomycin (30 µg) antibiotics. Lycopene was extracted from Tomato (*Lycopersicon esculentum*) and further subjected to prepared different concentrations (25 µL, 50 µL, 75 µL, and 100 µL) of lycopene extract.<sup>8</sup> The antibacterial activity of different concentrations of the prepared lycopene extract was evaluated employing an agar-well diffusion assay against five drug-resistant bacterial strains.<sup>8</sup> Antimicrobial activity for the different concentrations was estimated by measuring the diameter of the zone of inhibition. Except for *S. aureus*, the antimicrobial activity for the other four bacteria increases consecutively with the increase in lycopene concentration.<sup>8</sup> The highest zone of inhibition was observed against *Proteus mirabilis* at 100 µL of lycopene concentration followed by *Escherichia coli* at 100 µL, *Pseudomonas aeruginosa* at 100 µL, *Klebsiella pneumonia* at 100 µL, and *Staphylococcus aureus* at the 75 µL lycopene concentration.<sup>8</sup> Stronger antibacterial activity of lycopene was observed against Gram-negative bacteria than the Gram-positive bacteria. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of lycopene extract were determined using agar broth dilution method with Mueller Hinton (Sigma-Aldrich) broth of 100 µL and serially diluted with 10 µL of bacterial inoculums (10<sup>6</sup> CFU/mL).<sup>8</sup> Tubes containing





Mueller Hinton Broth and 100 µl of inoculum were prepared as the negative control. Lycopene extract was further diluted to 10 µg/ml - 500 µg/ml in concentrations using Muller Hinton broth and that shows the results for the MIC and MBC ranged from 50 and 125 µg/mL.<sup>8</sup> The lowest minimum inhibitory concentrations, 50 µg/ml was noted for *E. coli* followed by 75 µg/ml for *Staphylococcus aureus*, 85 µg/ml for *Proteus mirabilis*, 95 µg/ml for *Klebsiella pneumonia*, and 125 µg/ml for *Pseudomonas aeruginosa*.<sup>8</sup>

Antibacterial activity and lycopene content of methanolic extracts of *Nasturtium officinale* were determined by Zafar et al. (2017). The extract showed antibacterial activity against two Gram-positive and two Gram-negative bacteria.<sup>4</sup> However, it was found less compared to the standard antibiotic (amoxicillin). *Bacillus cereus* was found more sensitive to the extract followed by *Escherichia coli*, *Enterococcus faecalis*, and *Klebsiella pneumonia*.<sup>4</sup> Minimum inhibitory concentration and minimum bactericidal concentration were also determined. It was found that the lycopene concentration is higher than the concentration of Chlorophyll b and β-carotene in the methanolic extracts of *Nasturtium officinale*.<sup>4</sup> These findings may open a new field of research in herbal drugs especially for antibiotic-resistant strains of certain bacteria.<sup>4</sup> Therefore the antibacterial activity of lycopene can be based for further in vivo investigation to counter many human diseases.

#### Lycopene in treatment of Chlamydial infection.

Chlamydial infection is caused by *C.pneumoniae* and *C.trachomatis*.<sup>15</sup> The bacteria falling in the family of Chlamydiaceae is known to cause a wide variety of diseases such as inflammatory disease of the eye, genitals, cardiovascular, and respiratory system.<sup>15</sup> The scope of the dependency of the Chlamydial developmental cycle on host cells gives an ample opportunity to regulate/control chlamydial species. Hence, by regulating the metabolic pathway of the host cell developmental process, the cycle of infecting species of chlamydia can also be regulated.<sup>15</sup> The study was done to test lycopene formulation in the prevention of chlamydial infection.<sup>15</sup> It revealed that Lycopene formulation prevented the chlamydial infection when the B10.MLM was treated with oil-formulated lycopene.<sup>15</sup> The expansion of *C. trachomatis* infection was inhibited which was mediated through dose-dependency.<sup>15</sup> When cells infected with *C. trachomatis* were treated with 0.125 to 0.5 mg/ml concentration of microencapsulated lycopene.<sup>15</sup> Then it was observed that the number of infected cells moderately decreased and also there was a reduction in the sizes of the inclusion bodies. When the patients were administered an oral dose of 7 mg Lycopene (single dose daily) for 4 weeks.<sup>15</sup> There was a gradual reduction of IgG antichlamydial antibodies in their serum. The above study has revealed that lycopene has the property to inhibit chlamydial infection caused by *C.pneumoniae* and *C.trachomatis*.<sup>15</sup>

#### Lycopene in treatment of Community-Acquired Pneumonia

CAP (Community-acquired pneumonia) is mainly caused due to pathogens such as *C. pneumoniae*, influenza A, *M. pneumoniae*, and *S. pneumoniae*.<sup>16</sup> The choice of antibiotic treatment depends upon the type of bacteria infecting the person. Studies suggest that the most common CAP causing agent is *Chlamydomphila pneumoniae*.<sup>16</sup> As the name suggests this disease is acquired to a healthy person from an infected person. The disease is acquired upon inhalation of droplets (pathogens suspended in air) from an infected person, the pathogen reaches the lungs to further develop the infection.<sup>16</sup> The various reports suggest a high mortality rate due to CAP (around 1 million deaths/year) in Asia. In this study, different modes of treatment were compared.<sup>16</sup>

#### Lycopene in treatment of CPP/ CP

Most commonly suggested long-term antibiotic therapy was not able to elucidate the etiology and pathogenesis of Chronic bacterial prostatitis (CBP) entirely.<sup>17</sup> The cause of the development of this condition is still uncertain. It involves a wide range of symptoms such as ejaculatory pain, pelvic region pain, sexual dysfunction, obstructive and irritative voiding symptoms, psycho-social maladjustments, and depression; are some of the symptoms.<sup>17</sup> It is difficult to treat CP (Chronic Prostatitis) and CPPS (Chronic Pelvic Pain Syndrome) conditions with a single therapeutic drug as there are a lot of complex networks of signals, etiological factors, and tissue responses involved in the development of this condition.<sup>17</sup> Therefore, a multimodal approach to the treatment is being studied and tested. There are a lot of complex diagnostic parameters involved which can be shortened to 'UPOINTS', thus, UPOINTS stands for **U**rinary, **P**sychosocial, **O**rgan-specific, **I**nfection, **N**eurological, and **M**uscle **T**enderness.<sup>17</sup>

Patients involved in the study were subjected to a full course of combination therapy in which 4 weeks of antibacterial therapy was administered and 6 months of combination therapy of drugs including (1) 10 mg Alfuzosin (as α-adrenoreceptor blockers) were daily administered. (2) 640mg/ day of *S. repens* extract was given. (3) A tablet with combined preparation of lycopene (10 mg/day), *S. repens* (640 mg/day), and selenium (100 µg/day) was given; SABA or serpens might be given with this or excluded.<sup>17</sup> There was a 57% reduction in pain scores of NIH-CPSI by the end of the therapy.<sup>17</sup> Also, a remarkable improvement in voiding symptoms was observed. When patients were treated with the combination of *S. repens*, lycopene, and selenium; then there was a marked improvement in their voiding symptoms.<sup>17</sup> This was not the case when only *S. repens* treatment was provided. In the treatment of CP/ CPPS fixed combination therapy was given which showed a remarkable improvement in all the above domains of patients could be achieved.<sup>17</sup> Thus, from this, it could be concluded that by only targeting these domains –U, O and I of UPOINTS, helped in subsiding the



symptoms of other related domains such as sexual functions in a substantial number of patients.<sup>17</sup> For relieving the symptoms, it was suggested that plant extract lacked efficacy, and the combination of *S. repens*, lycopene, and selenium is more active.<sup>18</sup> In the treatment of CP, it was noted that uropathogens can be best treated with combination therapy of fluoroquinolone-macrolide drugs rather than a single-drug treatment.<sup>19</sup> Also, for the very first time macrolides have been recommended to treat chronic prostatitis syndrome. Macrolides are recommended for their following property- 1. they have a great prostatic penetration ability.<sup>18</sup> They work excellently on sexually transmitted and intracellular pathogens.<sup>18</sup>

C.H. Han et al. (2008) had taken an approach to assess the role of lycopene to improve the treatment efficacy of CBP. The CBP rat model had been developed and treated with ciprofloxacin or lycopene, or both to evaluate the therapeutic effect of lycopene.<sup>20</sup> Following two weeks of treatment, findings of microbiological cultures of the prostate tissue and urine cultures as well as histological findings of the prostate were analyzed. Out of 74 rats, CBP was developed in 45 rats, which were then consecutively divided into Four groups: 1) control group (n=10) was administered 1mL of phosphate-buffered saline (PBS), 2) lycopene treatment group (n = 11) was administered 9 mg/kg body weight of lycopene, 3) ciprofloxacin treatment group (n = 11) was administered 2.5 mg/kg body weight of ciprofloxacin, 4) lycopene/ciprofloxacin group (n = 13) was administered 2.5 mg/kg body weight of ciprofloxacin.<sup>20</sup> Microbiological and histological studies on CBP rats conducted by C.H. Han et al. (2008) revealed that prostatic inflammation and bacterial growth (CFU count) in the lycopene-treated rates were slightly lower than those of control rats.<sup>20</sup> However, no statistically significant differences in the parameters were found. Ciprofloxacin can diffuse into the extracellular fluid as well as into cells and exhibits good antimicrobial activity against most uropathogens. This may cause both ciprofloxacin and lycopene/ciprofloxacin-treated rats to show a significant reduction in bacterial counts and improvement of inflammation compared with control rats. Moreover, CFU count and inflammatory changes decrease rapidly in rats treated with lycopene/ciprofloxacin compared with ciprofloxacin or lycopene alone that denote the tendency towards improvement.<sup>20</sup> A synergistic effect was noticed when lycopene was used together with ciprofloxacin. Hence, combination therapy of fluoroquinolone and lycopene can improve the treatment efficacy of CBP.<sup>20</sup> However, more appropriate clinical studies should be carried out to elucidate the exact mechanism of action of lycopene will be necessary.

#### Cardioprotective effects of Lycopene.

A macrolide is a group of antibiotics that are used to treat soft tissue or respiratory bacterial infection.<sup>20</sup> To this, tulathromycin is also a vital macrolide that is used widely to treat respiratory infection caused by gram-positive bacteria (in swine and cattle).<sup>20</sup> But the usage of

tulathromycin is also a cause of concern as it results in cardiotoxic effects. This effect arises as tulathromycin leads to enhanced production of ROS (reactive oxygen species) and changes the serum levels of ionized calcium, coagulation factors, and potassium.<sup>20</sup> Likewise, DFS (Diclofenac sodium) is a potential NSAID drug (non-steroidal anti-inflammatory drug) that stops the formation of pro-inflammatory prostaglandins by inhibiting the COX-2 enzyme (cyclo-oxygenase-2).<sup>20</sup> Also, it is a known fact that when NSAID is given in combination with an antibiotic it helps in improving the inflammation and controlling the proliferation of pathogens. But prolonged intake of DFS can also lead to cardiotoxic effects (such as congestive heart failure or myocardial infarction). Further, it has been reported that lycopene (acyclic carotenoid) possesses cardioprotective properties along with being anti-inflammatory, antioxidant, and antimicrobial.<sup>20</sup>

The study was conducted on Swiss albino mice. These mice were divided into 7 groups (8 in each group), and they were subjected to different treatments.<sup>20</sup> After the completion of the study, it was observed that when DFS and tulathromycin are consumed as a single dose or in combination then the following changes occurred (as compared to the controlled group)- LDH (lactic acid dehydrogenase) level got enhanced, CK (creatin kinase) levels got increased, CK-MB (Creatine kinase-myocardial B fraction) serum level got significantly increased, CTnT (Cardiac troponin) levels were elevated, the higher extent of cardiac tissue levels of NO and MDA, significant drop in the GSH concentration of cardiac tissue, TAC and action of other compounds such as SOD, GPx and CAT enzymes were noted.<sup>20</sup>

#### Lycopene and Atherosclerosis

Atherosclerosis is a condition in which fatty compounds get deposited in the inner wall of the arteries. Cardiovascular disease is a cause of concern as it has caused major mortality and morbidity in people across the developed societies, there is a considerable rise in cases in developing countries as well.<sup>21</sup> Although cardiovascular diseases have been extensively researched and studied still this disease is the cause of nearly half of the deaths in Europe. It has been estimated in a report that 2 million people in the European Union (EU) would lose their lives owing to this disease and also, it costs 192 billion euros each year. Not only is the mortality rate worrisome, but this has also caused a loss in informal care costs by 22% and productivity rate by 21%.<sup>21</sup> This has emerged as an unprecedented challenge for the economies of the EU. Various studies have been conducted to study and know the contribution of lycopene in atherosclerosis prevention. The studies have shown that the build-up of oxLDL levels is due to oxidative stress.<sup>21</sup> This stress results due to an imbalance of antioxidant and oxidant levels. There is proof that antioxidants help in protecting and preventing the condition of atherosclerosis.<sup>21</sup> Thus, the consumption of lycopene (dietary carotenoid acting as an antioxidant) and its supplements in daily diets helps in keeping



atherosclerosis at bay.<sup>21</sup> The studies suggest that by maintaining a good lifestyle and a healthy diet (along with daily consumption of lycopene), the progression of atherosclerosis could be controlled and inhibited.<sup>21</sup>

### Neuroprotective effects of Lycopene

#### Neuroprotective effects of lycopene in Neurodegenerative diseases.

Alzheimer's and Parkinson's Disease are very common neurodegenerative disorders characterized by memory loss and tremors respectively along with cognition and behavioral impairment. Lycopene has been found to inhibit oxidative stress in both disorders. A study revealed that Lycopene treatment of dose 5 mg/kg for up to 8 weeks can reduce *tau* phosphorylation in the brain tissues of P301L transgenic mice.<sup>1</sup> This suggests that inhibition of *tau* protein phosphorylation may facilitate the anti-Alzheimer's effect of Lycopene. Similarly, another study proved that Parkinson's inducing stimuli from the dopaminergic neurons can be reduced by lycopene supplementation.<sup>1</sup> "The anti-parkinson's effect of lycopene may be mediated by reducing neuronal apoptosis."<sup>1</sup> However, the inhibition of neuronal apoptosis by lycopene remains unknown. Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disease of CNS.<sup>1</sup> Fifteen days of lycopene treatment (10 mg/kg) has been shown to reverse 3-nitropropionic acid (3-NP)-induced mitochondrial dysfunction and oxidative stress, including the decrease in mitochondrial complexes-II, IV, and V activity; the reduction in mitochondrial respiration; the increase in mitochondrial lipid peroxidation and ROS/nitric oxide (NO) levels; and the decrease in superoxide dismutase (SOD) activity and thiol content in brain tissues. These mechanisms facilitate the behavior improvement effect of lycopene in 3-NP-induced HD.<sup>1</sup> This strongly indicates that lycopene supplementation may be beneficial to ameliorate HD symptoms.

#### Neuroprotective effects of lycopene in subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) is a severe disease in the CNS that features brain edema and BBB disruption. A study conducted revealed that acute lycopene treatment for about 2 hours with the dose of 40 mg/kg after the construction of the SAH model ameliorates SAH-induced disruption in Blood-Brain Barrier, increase in brain water content, and neurological deficits in SD rats via attenuation of neuronal apoptosis and pro-inflammatory response in the cortex.<sup>1</sup>

#### Neuroprotective effects of lycopene in cerebral ischemia

Cerebral ischemia is a leading cause of cerebrovascular disease that is characterized by an increase in oxidative stress markers, such as MDA and reactive oxygen species (ROS), as an important course of ischemic brain injury.<sup>1</sup> Lycopene may protect the neurons against ischemic injury by inhibiting neuronal apoptosis. Pre-treatment of mice

with lycopene for approximately 14 days can suppress a hepcidin-mediated decrease in ferroportin, a sole iron transporter, thereby reducing the brain infarction volume and improving the neuro-behaviours in rats, which may be associated with the change in iron regulating proteins.<sup>1</sup>

#### Neuroprotective effects of lycopene in seizure

Epilepsy is one of the most predominant neurological disorders generally facilitated by mitochondria-mediated oxidative stress. It can promote the production of ROS and oxidation of biomolecules (proteins/lipids/nucleotides), thereby increasing the susceptibility of the brain to pro-epileptic stimuli through impairing mitochondrial bioenergetics.<sup>1</sup> In a study conducted, Laca mice were given a long term Lycopene treatment for about 29 days at the dose of 5-10 mg/kg which has been shown to prevent kindling epilepsy via reversal pentylentetrazol (PTZ)-induced oxidative damage as well as impairment in mitochondrial enzyme complex I, II, and IV activities.<sup>1</sup>

#### Antidepressant-like effects of lycopene

A study proved that 7 days of lycopene pre-treatment of about 60 mg/kg can reverse LPS-induced depression-like behaviours in the tail suspension test and forced swim test in mice, suggesting that lycopene may be a potential antidepressant.<sup>1</sup> The inhibitory effect of lycopene on LPS-induced increase in pro-inflammatory cytokines in serum and hippocampus is highly in accordance with the neuroinflammation hypothesis of depression.<sup>1</sup>

#### Neuroprotective effects of lycopene on cognition and memory impairment induced by different factors

*Diabetes-associated cognitive impairment* – "10 weeks of lycopene treatment at the dose of 1, 2, and 4 mg/kg has been shown to attenuate cognitive impairment in streptozotocin (STZ)-induced diabetic rats in a dose-dependent manner via (i) decreasing acetylcholinesterase activity, (ii) reducing the levels of thiobarbituric acid-reactive substances, (iii) increasing the enzymatic activities of SOD and CAT, and (iv) reducing NO levels in the cerebral cortex and/or hippocampus".<sup>1</sup> Neuroprotective effects of lycopene may be facilitated by the regulation of blood glucose levels.

*Colchicine-associated memory impairment* – "Chronic lycopene treatment (2.5 or 5 mg/kg) at different time points has been shown to reverse colchicine-induced memory impairment via inhibition of oxidative stress and neuroinflammation, which is indicated by reversal of colchicine-induced (i) increase in MDA and NO levels, (ii) reduction in SOD, CAT, and GSH levels, (iii) impairment in mitochondrial respiratory enzymes (cytochrome oxidase, succinate dehydrogenase, and NADH dehydrogenase), (iv) increase in caspase-3 activity and decrease in cell viabilities, (v) increase in AChE activity, and (vi) increase in pro-inflammatory cytokine levels in hippocampus and cortex".<sup>1</sup>

*High fat-associated cognitive impairment via inhibiting spine loss, oxidative stress, and neuroinflammation* – "3





weeks of lycopene treatment (4 mg/kg) has been shown to suppress HFD-induced impairment in working, spatial, and object recognition memory in rats, suggesting that lycopene is a potential agent that improves cognitive performance".<sup>1</sup> "Chronic lycopene treatment (21 days) has been shown to inhibit the hypercholesterolemic diet-induced increase in pro-inflammatory cytokine, glutamate, N-methyl-D-aspartic acid (NMDA), and dopamine levels, as well as hypercholesterolemic diet-induced decrease in GABA and serotonin (5-HT) levels, in rat brain tissues, suggesting that lycopene may be a candidate for that purpose".<sup>1</sup>

*D-galactose-induced cognitive impairment* – "Two months of lycopene supplementation (0.03%, w/w, mixed with standard, about 50 mg/kg) has been shown to reverse D-galactose-induced cognitive impairment via reversal of neuronal degeneration and nucleus shrinkage in CD-1 mouse hippocampus, suggesting that lycopene indeed has anti-aging activities".<sup>1</sup>

#### Inhibitory effects of lycopene on toxic factors-induced neurotoxicity

*Inhibition of monosodium glutamate (MSG)-induced neurotoxicity in rats* – Lycopene-MSG co-administration may be a potential approach for MSG-induced neurotoxicity amelioration. It has been proved that Chronic lycopene treatment rebalanced the pro-and anti-apoptotic signaling in brain tissues in MSG-challenged rats. This includes the increase in anti-apoptotic Bcl-2 levels and the decrease in pro-apoptotic Bax levels. The whole process may help restore brain homeostasis.<sup>1</sup>

*Inhibition of trimethyltin (TMT)-induced neurotoxicity in primary cultured rat hippocampal neurons* – Lycopene pre-treatment (1  $\mu$ M) results in prevention of TMT-induced cellular apoptosis in primary cultured rat hippocampal neurons. It suggests the probability of using lycopene as a potential agent for the treatment of neurodegenerative disorders.<sup>1</sup>

*Inhibition of heavy metal-induced neurotoxicity in cultured neurons* – Methylmercury (MeHg), a highly toxic chemical pollutant, induces neuronal damages in both immature and mature brain tissues through mechanisms ranging from disruption of Ca<sup>2+</sup> homeostasis to glutamate homeostasis, that subsequently activates severe oxidative stress.<sup>1</sup> Lycopene pre-treatment (doses of 1, 5, and 10  $\mu$ M) has been shown to improve cell viability in cerebellar granule neurons of MeHg-treated primary cultured rats in a dose-dependent manner.<sup>1</sup> On the other hand, in vivo (10  $\mu$ M, 24 h) and in vitro (5 mg/kg, 21 days) lycopene treatment has been shown to reverse hippocampal cell toxicity and Cd-induced hippocampal dystrophy as suggestive prevention or treatment of cadmium (Cd)-induced neurotoxicity.<sup>1</sup>

*Inhibition of tert-butyl hydroperoxide-induced neurotoxicity via promotion of the secretion from neural stem cells* – Neural stem cells (NSCs) are the self-renewing precursors of neurons, oligodendrocytes, and astrocytes,

and in recent years, good potential for the treatment of AD and PD.<sup>1</sup> "Lycopene pre-treatment (2  $\mu$ M) has been shown to promote the secretion of BDNF, NGF, and VEGF from NSCs, and the lycopene-treated-NSC-conditioned media (Ly NSC-CM) containing these factors has been shown to attenuate tert butyl hydroperoxide (t-BHP)-induced cellular apoptosis in primary cultured cerebral cortical neurons, suggesting that lycopene may be suitable for augmentation of the therapeutic efficacy of NSCs".<sup>1</sup>

#### Neuroprotective effects of lycopene in other pathological conditions in the CNS

*Protection of rats against haloperidol-induced orofacial dyskinesia* – "Long-term (21 days) lycopene treatment at the dose of 5 and 10 mg/kg has been shown to ameliorate vacuous chewing movements, tongue protrusions, and facial jerking in haloperidol-treated rats, and reverse the haloperidol-induced decrease in motor activity, as well as an increase in latency and foot, slips on narrow beam walking apparatus in rats, suggesting that lycopene supplementation may be a potential choice for the treatment of orofacial dyskinesia in schizophrenic patients".<sup>1</sup> "21 days of lycopene treatment also prevents a haloperidol-induced increase in proinflammatory cytokines in the striatum, suggesting that inhibition of neuroinflammation may be involved in the therapeutic effect of lycopene in orofacial dyskinesia".<sup>1</sup>

*Inhibition of ethanol-induced nicotinamide adenine dinucleotide depletion in human astrocytes* – Excessive alcohol exposure can induce cognitive dysfunction and reduction of brain volume in humans. "Lycopene pre-treatment (5 and 10  $\mu$ M) was found to reverse ethanol-induced increase in poly (ADP-ribose) levels as well as ethanol-induced decrease in nicotinamide adenine dinucleotide (NAD<sup>+</sup>) levels in human U251 astrogloma cells and primary human astrocytes".<sup>1</sup> "The effect of lycopene in the restoration of NAD<sup>+</sup> levels in human astrocytes not only makes the astrocytes acquire enough ATP but helps to maintain the activity of sirtuin 1 (SIRT1)".<sup>1</sup>

#### **CONCLUSION**

This research review's purpose is to help the reader understand different aspects posed by the research on the therapeutic applications of Lycopene in different diseases and disorders. This is significant because it gives insights into the prevalence of the use of Lycopene as a neuroprotective, cardioprotective, antimicrobial, and prime option in the treatment of CP/ CPP. There has been much research and discussion conducted on these opinions of surveys, diagnostic procedures, and several types of treatment options. Most of the research found was on the potential benefits of lycopene in treating a whole range of disorders. More research and testing are required to gain a better understanding of the appropriate dosage forms and supplementation in order to be the all-in-one phytochemical treatment option for various illnesses in humans. Just as lycopene is known to act as an antioxidant and antimicrobial, in a similar way another



naturally occurring compound derived from *Ficus sycomorus* Linn was extracted and studied for its potential role to act as an antioxidant and an antimicrobial agent.

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Not applicable.

#### Human and Animal Rights

No Animals/Humans were used for studies that are the basis of this research.

#### Consent for Publication

Not applicable.

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The author confirms that the data supporting the findings of this research are available within the article.

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