

# **RESEARCH ARTICLE**

# LYCOPENE EFFICACY TOWARDS STREPTOZOTOCIN INDUCE COGNITIVE DYSFUNCTION: A PRELIMINARY POSSIBLE FUTURE ALTERNATIVE FOR NEUROLOGICAL AILMENTS

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Lycopene; Despair test; Light and dark simulation; Streptozotocin; Cognitive Dysfunction

#### Abstract

..... Lycopene, a red-colored carotenoid, established for its antioxidant potentials towards cognitive dysfunction, a predictor of neurological maladies. Plentiful research in arena emphasizing towards formulation advancement and dose adjustment, inclining to impart an edge for lycopene biopotentials, but still leaving a lag. Current preliminary research emphasizes on therapeutic potentials of lycopene over cognitive dysfunction at certain doses established via behavioral models. Lycopene 100mg/kg dose depicted a significant immobility time curtail to 53.33±4.356secs in despair Test (DT), 25.67±2.028 crossing in Light and dark (LD) simulation, and 22.67±1.116 rotations in manual rota-wheels(RW) design respectively, in contrast to STZ 83.50±4.766 14.67±1.764 control sec (DT), (RD) and 9.333±1.606(RW) respectively. Lycopene 100 mg/kg dose depicted positive and impressive results against cognitive dysfunction. Prospectively, Lycopene could be utilized as an alternative supplement for neurological diseases.

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#### Introduction:-

Lycopene, a red-colored carotenoid recognized for antioxidant potentials. Being an effective radical scavenger, it owes for various neurological activities. Cognitive dysfunction is a designated predictor of any neurological disease[1]. Several studies conducted where cognitive dysfunction was evaluated to correlate depression, Epilepsy, Alzheimer's, Parkinson's, and other neurological ailments[2-5]. Oxidative-stress (OS), a designated source of neurological diseases instigated by endogenic antioxidant system accompanied by cognitive dysfunction. OS generated ROS oxidizes brain macro-molecules and reported a trigger of cognitive abnormalities. Lycopene adopts several antioxidant mechanisms to decrease oxidative stress but due to diminished bioavailability, it fails to express its potential[2-5]. Although Lycopene shown a lipophilic characteristic due to conjugated system, but its high molecular weight ( $C_{40}H_{56}$ =536.87 g/mol) limits its bioavailability. Geometrical isomerism influences its bioavailability as *cis*-isomers impart thermal stability and higher absorption rate in humans [6, 7]. Lycopene absorption also varied with age and diet type, affecting its bioavailability[8][9]with a half-life of 2-3 days[10]. Besides liver it accumulates in adipose tissues, kidneys, lungs, and other lipid-containing organs[6, 7]. Several toxicity studies suggested appropriate dose of 5-10 mg/kg, but no toxic effects noticed in rats administered 3 g/kg/day [11]. Cognitive dysfunction is a designated hallmark of diabetic patient hence artificial diabetes develops in rats via streptozotocin (STZ) to gain cognitive model[12]. STZ acts by activating GTS and further favoring superoxide radicals  $(O_2^{\circ})$  generation (Figure 1). Plentiful research is still in arena emphasizing formulation

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development and dose adjustment to impart an edge for lycopene bio-potentials, but still leaving a lag. Current preliminary research emphasizes on therapeutic potentials of lycopene over cognitive dysfunction at certain doses established via behavioral models.

## **Materials and Methods:-**

#### Materials:

Streptozotocin, Lycopene, Hamilton micro-syringe, 27G needle, citrate buffer, distilled Water procured from Sigma Aldrich, USA, mice food pellet was obtained from local distributor.

#### **Invivo Experiment:**

Six groups of 6 albino mice were approved by the institutional ethical committee. Albino mice (20 to 25 gm) were domesticated as standard guidelines (25°C, light, and dark diurnal 12/12 hrs cycle, appropriate food and water)[13].

#### Streptozotocin (STZ) engendered Cognitive dysfunction (SCD)[14]:

STZ administered in mice via anesthetizing by isoflurane through i.c.v. route by 27G needle, 25  $\mu$ l Hamilton microsyringe interleaved perpendicular (2 mm) through skull in particular coordinates (Figure 1). STZ-Controlled group delivered STZ i.c.v.(0.1 mg/site, 4  $\mu$ l citrate buffer) at 1 and 48 hrs to gain Cognitive dysfunction[15].

#### **Dosing:**

SCD encompassed 6 groups of 6 animals (already STZ engendered), received lycopene in 0, 10, 50, 100, 150, 200 mg/kg dose via intraperitoneal route in tween-80 suspension. Cognitive activity was measured via Despair test, manual rota-wheel, and Light and dark simulation, 45 minutes post-drug administration. Readings were taken individually and back-to-back switching from one to another model.

#### **Despair Test (DT):**

Animals were forcefully made swim (15 minutes) in Water-filled (Ht=10 cm) Plexiglass cylinder (Ht=25, Dia=10 cm) at 25°C. Total immobility duration (no struggling and float motionless) was gauged during 15 mins[16].

#### Light and dark simulation (RD):

Animal cage  $(44 \times 21 \times 21 \text{ cm})$  was darkened  $1/3^{rd}$  black (spray paint),  $1/3^{rd}$ , and other  $1/3^{rd}$  was kept in bright LED. Number of crossing from dark to light and vice versa was evaluated in 15 minutes.

#### Manual Rota-wheel Design (RW):

Animals could rotate wheel, diameter15 cm and thickness 4cm, rotating at their free will, rotations number were assessed in 10 minutes.

#### **Statistical Assessment:**

Statistical assessment was handled via one-way analysis of variance (ANOVA) pursued through Dunnett's test. P<0.05, deemed designated as statistically significant, using Graphpad (V9, LLC, USA)

#### **Result and Discussion:-**

Lycopene a red, structurally open-chain isomer of  $\beta$ -carotene comprising conjugated (11) and unconjugated (2) double bonds system which imparts a tremendous antioxidant activity towards OS. OS contributes to development of several chronic neurological ailments. Antioxidants act by scavenging free radicals or reactive-oxygen species (ROS), relieving neurodegeneration. Brain often requires consistent oxygen supply and possibly culprit to ROS generation during fail response of intrinsic anti-oxidation system, heading to OS. Intrinsic antioxidant system failure implies improper ROS generation and counteraction[17,18]. Intrinsic oxidases are liable for superoxide radical production, further metabolized to H<sub>2</sub>O<sub>2</sub> and water by other oxidases and peroxidases[19-22]. STZ actuates neuron's glutamatergic-Transmitter for generation of ROS (Figure-1)[21, 23].

Lycopene scavenges singlet and excited oxygen species and also acts by restoring the functioning of antioxidant enzymes[24], reducing oxidative damage to DNA and biomolecules[25]. Several studies confirmed the safe doses of lycopene as 75 mg/day or ranging 10-120 mg/day. Intake spans prescribed from country to country as 3.7-16.15 mg United States, Germany 0.7-1.3 mg, Canada of 25.2 mg etc.[27]. DT, LD simulation, and RW design are perfect

models for Cognitive assessment. DT assess brain alertness reflects by immobility, cognition impairment, accomplishing fast results with high validity and reliability.

_represented as p<****0.0001,***0.001,**0.01,*0.05) contrasted to control group via ANOVA post Dunnett's test.				
Group	Treatment	DT	LD simulation (no of	RW Design (No of
No.			crossing)	rotations)
1	STZ control	83.50±4.766	14.67±1.764	9.333±1.606
2	STZ+10 mg/kg Lyc	69.83±5.009	14.33±1.606	9.833±1.470
3	STZ+50 mg/kg Lyc	64.33±4.240*	22.67±1.944*	15.50±1.478****
4	STZ+100 mg/kg Lyc	55.67±2.362**	25.67±2.028***	22.67±1.116**
5	STZ+150 mg/kg Lyc	53.33±4.356***	19.67±1.820	19.33±3.138***
6	STZ+200 mg/kg Lyc	51.83±6.431***	20.00±1.211	22.50±1.607

Table 1:-Lycopene dose 0, 10, 50, 100, 150, 200 mg/kg evaluation. Results expressed in Mean±SEM, Significance
represented as p<****0.0001,***0.001,**0.01,*0.05) contrasted to control group via ANOVA post Dunnett's test.



Figure 1:-Oxidative stress Series: A. streptozotocin mechanism in OS development, B. Lycopene ROS scavenging mechanism against OS engendered Cognitive dysfunction

Lycopene dose at 100, 150, and 200 mg/kg predicted a significant immobility time decrement of  $55.67\pm2.362$ ,  $53.33\pm4.356$ ,  $51.83\pm6.431$  secs respectively, contrasting with STZ control ( $83.50\pm4.766$  sec) (Figure-2, Table-1). LD simulation established on light and dark environment exploration. Neuroactive drugs increase crossing number between dark and light compartments. LD simulation often uses to gauge learning, anxiety, and exploration, rodents. LD also employed to test impulsivity, neural systems relevancy. Number of crossing from light to dark or contrariwise for 10 minutes counted as parameter[28]. Lycopene dose at 50 and 100 mg/kg showed a significant crossing number of  $22.67\pm1.944$ , and  $25.67\pm2.028$  respectively, contrasting with STZ control ( $14.67\pm1.764$ ) (Figure-2, Table-1). RW functions like LD simulation, mostly neuroactive drugs increase rotation numbers. Lycopene dose (mg/kg) at 100, 150 and 200 predicted significant rotation number of  $15.50\pm1.478$ ,  $22.67\pm1.116$ , and  $19.33\pm3.138$  respectively contrasting with STZ control ( $9.333\pm1.606$ ) (Figure-2, Table-1). Overall representation proved Lycopene as a neuroactive drug. 10 mg/kg dose didn't show appropriate response, whereas 50 had shown some but dose (mg/kg)100, 150 and 200 demonstrated a significant result but as almost close responses. Safe dose range of lycopene reported 10-120 mg/kg, thus we conclude 100 mg/kg dose of lycopene as effective against cognitive dysfunction.



**Figure 2** A:-Despair test, (parameter: immobility time in seconds/5 minutes, B. Light and dark simulation, (Parameter: crossing number/10 minutes), C. Manual rota-wheel design (Parameter: number of rotation/10 minutes). Results expressed in Mean±SEM, Significance represented as p<\*\*\*\*0.0001,\*\*\*0.001,\*\*0.01,\*0.05) contrasted to control group via ANOVA post-Dunnett's test

# **Conclusion:-**

Lycopene 100 mg/kg dose depicted positive and impressive results in cognitive dysfunction. Lycopene proposed on acting over Oxidative cascade, intrinsic oxidases, and peroxidases. Like other polyene antioxidants like curcumin, Carotenoids, and piperine, lycopene might also share similar neuroactivity. Lycopene can be employed as an alternative supplement for neurological diseases.

# **Disclosure:-**

Author states of no conflict of interest

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