

# Fenugreek (Trigonella Foenum-Graecum) and its Active Compounds: A Review of its Effects on Human Health through Modulating Biological Activities

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## ABSTRACT

Fenugreek seed are rich sources of various essential compounds and such components shows a significant role in the diseases cure and management through its anti-inflammatory, hepatoprotective, cardioprotective, neuroprotective, immunomodulatory, nephroprotective and anti-microbial activity. Moreover, fenugreek seed is a rich source of antioxidant and such potentiality inhibit the pathogenesis of diseases through free radical scavenging activity. Besides, fenugreek and its active compound shows role in tumour inhibition through modulating various genes activity including induction of apoptosis, tumour suppressor gene and inhibition of tumor necrosis factor. This review comprehensively summarizes the role of fenugreek seeds in health management through modulating various physiological and biochemical activities, along with special emphasis on *in vitro* and *in vivo* study.

**Key words:** Fenugreek, Trigonella foenum-graecum, Anti-oxidant, Anti-inflammatory, Health management, Anti-cancer activity.

## INTRODUCTION

Fenugreek (Trigonella foenum-graecum) is a plant of family fabaceae and it is used as a dietary supplement and very useful in the management of diabetes atherosclerosis, liver protection, cardioprotective and renal protection. Moreover, fenugreek seed are rich sources of various essential compounds and these components play a significant role in the diseases cure and management through regulation various biological activities. Fenugreek seed is a rich source of antioxidant and such potentiality inhibit the pathogenesis through free radical scavenging activity. Fenugreek therapeutic role evidences as pre-treatment of herbal extract restored activities of all the enzymes and therefore displayed a total protective effect on additive effect of cyclophosphamide and L-buthionine-SR-sulfoximine. Restoration of glutathione by extract treatment might show a significant role in backing cyclophosphamide -induced apoptosis and free radical-mediated lipid peroxidation in urinary bladder.<sup>1</sup> Fenugreek play a vital role in the inhibition of inflammation and fenugreek seeds by determining the lipid peroxidation and cyclooxygenase enzyme inhibitory activities of their various types of extract. The extracts inhibited lipid peroxidation, cyclooxygenase enzyme -1 and cyclooxygenase enzyme -2. Moreover, isolates, without the saccharides, inhibited lipid peroxidation and cyclooxygenase enzyme -1 and -2 enzymes.<sup>2</sup> The hepatoprotective effect of the ethanolic extract of Fenugreek seeds against CCl<sub>4</sub> induced liver damage in rats was examined. Result revealed that extract of Fenugreek seeds showed highly hepatoprotective effect against carbon tetrachloride induced-necrosis with less effect against fatty

changes, this could be due to the antioxidant action of the active constituents in the extract that counteract and scavenge the intermediates free radicals of carbon tetrachloride.<sup>3</sup> The immunomodulatory activity of ethanolic extract of Fenugreek was studied for phagocytic activity, cell mediated and humoral immune system based on mice model. Fenugreek showed considerably high phagocytic index against control group, demonstrating stimulation of the reticulo-endothelial system. Substantial decrease in mean difference, in the foot paw thickness in DTH indicates its anti-inflammatory activity. Fenugreek play a significant role in the managemnt of cancer through modulating various cell signalling pathways. Diosgenin , an active compound of fenugreek inhibits receptor-activated nuclear factor-kappaB ligand-induced osteoclastogenesis, suppresses tumor necrosis factor-induced invasion, and blocks the proliferation of tumor cells. Finally, study propose that diosgenin suppresses proliferation, inhibits invasion, and suppresses osteoclastogenesis via inhibition of NF-kappaB-regulated gene expression and enhances apoptosis.<sup>4</sup> Another study based on a mouse xenograft model reported that a combination of Thymoquinone and diosgenin meaningfully reduced tumor volume, mass as well as increased apoptosis. Thymoquinone and diosgenin, alone and in combination, inhibit cell proliferation as well as induce apoptosis in squamous cell carcinoma. The combination of Thymoquinone and diosgenin is a potential antineoplastic therapy in this common skin cancer.<sup>5</sup>

## INGREDIENTS OF FENUGREEK SEED

Fenugreek seed are rich sources of various essential compounds and these components play a significant

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role in the diseases cure and management through regulation various biological activities. The ingredients found in fenugreek seed are galactomannan, sapogenin, trigonelline, and 4-hydroxyisoleucine that have the anti-diabetic properties as well as shows role in the treatment of breast cancer.<sup>6</sup> Fenugreek holds 23–26% protein, 6–7% fat as well as 58% carbohydrates of which around 25% is dietary fibre,<sup>7</sup> and seeds are a rich source of fiber mainly non-starch polysaccharides.<sup>8</sup> Moreover, seed of fenugreek are rich in proteins such as globulin, lecithin and albumin<sup>9,10</sup> and also contain iron, comprising 33 mg/100 g dry weight<sup>11</sup> and unsaturated fatty acids,<sup>12</sup> flavonoids, and polyphenolic substances<sup>13,14</sup> and vitamins and calcium.

## MECHANISM OF ACTION OF FENUGREEK

Fenugreek seed are mixtures of numerous compounds such as alkaloids, proteins, carbohydrate, fiber and these compound play a vital role in the inhibition of various types of pathogenesis. Fenugreek seed is a rich source of antioxidant and such potentiality inhibit the pathogenesis through free radical scavenging activity. Fenugreek therapeutic role evidences as pre-treatment of herbal extract restored activities of all the enzymes and therefore displayed a total protective effect on additive effect of cyclophosphamide and L-buthionine-SR-sulfoximine. Restoration of glutathione by extract treatment might show a significant role in backing cyclophosphamide -induced apoptosis and free radical-mediated lipid peroxidation in urinary bladder.<sup>1</sup> Chronic inflammation may increase the risk of various diseases, such as cancers, rheumatoid arthritis and other diseases. However, its regulation is a key step towards inhibition of pathogenesis. In this context, fenugreek play pivotal role in the inhibition of pathogenesis through its anti-inflammatory activity. Fenugreek seed proved role in the inflammation as inhibition of edema by the plant extract at doses of 100 and 200 mg/kg and activity of the plant at doses of 100 and 200 was not significantly different from those of ibuprofen and dexamethasone. Among the prepared formulations of the plant, 3 and 5% creams of the fenugreek showed the most inhibition of edema which were not significant from hydrocortisone ointment.<sup>15</sup> Fenugreek seed also shows an important role in the management of diabetes and it was explained as mechanism of action of seeds of fenugreek was investigated in alloxan induced subdiabetic. The treatment showed substantial reduction of the glucose tolerance curve as well as improvement in the glucose induced insulin response, proposing that the hypoglycaemic effect might be mediated via stimulating insulin synthesis and/or secretion from the beta pancreatic cells of Langerhans.<sup>16</sup> Moreover, fenugreek seeds play role in the inhibition of tumour growth through modulating various activities including cell signalling pathways. Fenugreek extract showed role in the decrease of the cell viability and cause the induction of early apoptotic changes including flipping of phosphatidylserine as well as decrease of mitochondrial membrane potential.<sup>17</sup> Fenugreek seed also play role in management of various diseases through hepatoprotective, anti-microbial, cardioprotective and neuroprotective effects.

## FENUGREEK SEED: ROLE IN DISEASES MANAGEMENT THROUGH MODULATING VARIOUS BIOLOGICAL ACTIVITIES

### Anti-oxidant activity

Several fractions of the germinated seeds were included to explore their antioxidant potential at various levels. An aqueous fraction of fenugreek displayed the maximum antioxidant activity compared with other fractions. This study discloses substantial antioxidant activity in germinated fenugreek seeds which might be due partly to the being there of flavonoids and polyphenols.<sup>18</sup> The role of fenugreek seeds on blood lipid peroxidation as well as antioxidant status in diabetic rats was investigated. In this study, it was observed

increased lipid peroxidation and changes in circulating antioxidants were noticed in the diabetic state. Supplementation of fenugreek seeds in the diet caused lowered lipid peroxidation and amount of glutathione and beta-carotene were increased and the alpha-tocopherol content was decreased. The study reveals that disturbed free radical metabolism in diabetic animals might be normalized by fenugreek seed supplementation in the diet.<sup>19</sup> Fenugreek seed oil was extracted and evaluated for its chemical compositions and antioxidant activity against (DPPH) and (ABTS<sup>•+</sup>) radicals, total phenolic content and total flavonoid content of the oil were also investigated. Result showed a total number of 23 chemical compounds were detected. Furthermore, the oil of fenugreek seed indicated a strong antioxidant radical scavenging activity against both DPPH and ABTS assays. The total phenolic content as well as total flavonoid content of the oil were  $38.97 \pm 0.34$  mg GAE/gram oil and  $14.417 \pm 0.23$  mg QE/ gram oil.<sup>20</sup> Crude extracts of fenugreek were prepared with different solvents such as methanol, ethanol, dichloromethane, acetone, hexane and ethyl acetate. The finding confirmed that all extracts of the fenugreek display antioxidant activity and findings propose that the fenugreek extracts might act as strong source of antioxidants.<sup>21</sup> Another study result revealed that *A. marmelos* showed the highest phenolic content followed by *T. foenum* and *C. sativum* whereas flavonoids contents are high in *T.foenum graecum* followed by *C. sativum* and *A. marmelos*. Antioxidant property was checked by reducing power, NBT assay and H<sub>2</sub>O<sub>2</sub> scavenging. *A. marmelos* displayed the highest reducing power followed by *C. sativum* and fenugreek but fenugreek exhibited the highest superoxide and free radical scavenging followed by *C. sativum* and *A. marmelos* respectively.<sup>22</sup>

### Anti-inflammatory activity

The anti-inflammatory as well as anti-arthritis activities of fenugreek seeds was examined. Result revealed that with 0.5 mL/kg fenugreek seed petroleum ether extract treatment, there was 37% and 85% reduction in inflammation of the paw in carrageenan and formaldehyde-induced paw edema. In complete Freund's adjuvant -induced arthritis, a biphasic increase in paw volume followed by decrease was seen. There was 42.5% reduction in the weight of cotton pellets and significant reductions in the elevated SGPT and ALP activities in serum and liver of fenugreek seed petroleum ether extract treated rats.<sup>23</sup> The inhibition of edema by the plant extract at doses of 100 and 200 mg/kg were meaningfully different from the control group. This activity of the plant at doses of 100 and 200 was not meaningfully different from those of ibuprofen and dexamethasone. Amongst the prepared formulations of the plant, 3 and 5% creams of the fenugreek showed the most inhibition of edema.<sup>23</sup> The functional food quality of fenugreek seeds by determining the lipid peroxidation (LPO) and cyclooxygenase enzyme (COX) inhibitory activities of their ethyl acetate, hexane, methanolic and water extracts was investigated. The extracts inhibited lipid peroxidation, cyclooxygenase enzyme -1 and cyclooxygenase enzyme -2. Moreover, isolates, without the saccharides, inhibited lipid peroxidation and cyclooxygenase enzyme -1 and -2 enzymes between the ranges of 8–89%, 4–51% and 15–70%, respectively, at 25 µg/ml.<sup>2</sup>

### Hepatoprotective effect

The hepatoprotective effect of the ethanolic extract of Fenugreek seeds against carbon tetrachloride induced liver damage in rats was examined. Result revealed that extract of Fenugreek seeds showed highly hepatoprotective effect against carbon tetrachloride induced-necrosis with less effect against fatty changes, this could be due to the antioxidant action of the active constituents in the extract that counteract and scavenge the intermediates free radicals of carbon tetrachloride.<sup>3</sup> The hepatoprotective effect of fenugreek seed polyphenolic extract against ethanol-induced hepatic injury and apoptosis in rats was evaluated. Chronic ethanol administration

produced liver damage that was established by the elevation of markers of liver dysfunction—liver function enzymes, lactate dehydrogenase, bilirubin and gamma-glutamyl transferase in plasma and reduction in liver glycogen. Ethanol administration resulted in adaptive induction of the activities of cytochrome p450 and cytochrome-b5 and reduction in cytochrome-c-reductase and Glutathione-S-transferase, a phase II enzyme. Treatment with extract restored the levels of markers of liver injury as well as alleviated the alterations in alcohol metabolizing and detoxification enzymes and the electron transport component cytochrome-c reductase.<sup>24</sup> The protective effects of aqueous extract of against carbon tetrachloride, induced hepatotoxicity in rats was examined. Result confirmed that carbon tetrachloride increased serum transaminases, hepatic lipid peroxidation and hepatic enzymatic antioxidants activities. Moreover, fenugreek aqueous extract improved the harmful effects of carbon tetrachloride and normalised all tested biomarkers toward the control values. Overall, study concluded that aqueous extract of fenugreek plays a protective role against carbon tetrachloride -induced liver damages in rats.<sup>25</sup> Fenugreek was evaluated for hepatoprotective and antioxidant influence in mice. Result revealed that activities of serum aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and alkaline phosphatase elevated with prolonged feeding of HCD. Activities of these enzymes were decreased in animals fed basal control/ fenugreek containing diets after initial exposure to HCD, and were prominent in fenugreek groups<sup>26</sup>

### Gastroprotective effect

The role of fenugreek seeds compared to omeprazole was examined on ethanol-induced gastric ulcer. Result demonstrated that aqueous extract and a gel fraction isolated from the seeds exhibited noteworthy ulcer protective effects. The cytoprotective effect of the seeds appeared to be not only due to the anti-secretory action but also to the effects on mucosal glycoproteins. The fenugreek seeds also prevented the rise in lipid peroxidation induced by ethanol seemingly by increasing antioxidant potential of the gastric mucosa thereby lowering mucosal injury.<sup>27</sup> The effect of fenugreek seeds compared with ranitidine was investigated on aspirin-induced gastric ulcer. Result revealed that gel fraction isolated from the seeds displayed important ulcer protective effect. The fenugreek seed gel also prevented the rise in lipid peroxidation induced through aspirin presumably via enhancing antioxidant potential of the gastric mucosa thus decreasing mucosal injury.<sup>28</sup> The effect of Fenugreek seed extract in Indomethacin induced gastric ulcer models was investigated. Finding revealed that fenugreek treated group showed a significant decrease in ulcer index as well as volume of gastric juice and acidity when compared to control positive group. Oxidative enzyme study designated a substantial increase in Catalase, *Superoxide dismutase* and *Glutathione* value in treated group when compared with control positive group.<sup>29</sup>

### Neuroprotective effect

The neuroprotective effect of fenugreek seed powder against aluminium chloride induced experimental AD model was examined. Administration of germinated fenugreek seed powder mixed with ground standard rat feed showed role in the protection of aluminium chloride induced memory and learning impairments, Al overload, acetylcholinesterase hyperactivity, amyloid  $\beta$  burden. Finding based on result confirm the neuroprotective effect of fenugreek seeds.<sup>30</sup> The effect of treatment with fenugreek seed extract on the function of sciatic nerves of neuropathic mice was assessed. Result confirm that neuropathy was induced in mice through pyridoxine intoxication. Then, animals were treated with 0.2, 2 and 20 mg/kg of hydro-alcoholic extract of fenugreek seeds and fenugreek showed anti neuropathic effect and restores the function of nerve fibers. Moreover, electrophysiological recordings stated that the highest rate of healing was occurred in 20

mg/kg fenugreek extract treated animals.<sup>31</sup> Another study was formed to identify and evaluated SFSE-T, a standardized hydroalcoholic extract of *Trigonella foenum-graecum* L. seeds in animal models of Parkinson's disease. The concentration of trigonelline in a test sample of SFSE-T was found to be 82%. SFSE-T showed a significant increase in the number of ipsilateral rotations as compared with vehicle control group when tested in 6-OHDA-induced unilateral lesioned rats.<sup>32</sup>

### Cardioprotective effect

Cardioprotective effect of fenugreek on isoproterenol- induced myocardial infarction based on *in vivo* and *in vitro* was examined. The results designated the cardioprotective effect that detected in rats received fenugreek and additionally isoproterenol showed significantly decreased levels of TBARS and enhanced the activities of both enzymatic and non-enzymatic antioxidants in myocardial infarcted rats when compared to groups received isoproterenol and group received fenugreek. Over all, based on finding study demonstrated that cardioprotective effect of fenugreek on lipid peroxidation and antioxidant defense system during isoproterenol-induced myocardial infarction in rats.<sup>33</sup> The cardioprotective effect of a combination of fenugreek seeds and garlic was assessed in hypercholesterolemic rats administered isoproterenol. Myocardial infarction was induced with isoproterenol injection. Moreover, increased circulatory troponin, changed activities of cardiac ATPases, increased serum iron and decreased ceruloplasmin established myocardial infarction. Elevated lipid peroxides accompanied with reduced antioxidant molecules caused by isoproterenol and change activities of antioxidant enzymes in serum and heart in induced myocardial necrosis were countered by dietary fenugreek, garlic, and fenugreek plus garlic.<sup>34</sup> The cardioprotective effect of dietary fibre-rich fenugreek seeds and garlic was evaluated both individually and in combination in isoproterenol induced myocardial infarcted rats. Result showed that dietary fenugreek, garlic or fenugreek plus garlic was found to improve the pathological changes in heart tissue and lipid abnormalities in serum and the heart, the beneficial effect being higher with the combination of fenugreek and garlic, invariably amounting to an additive effect.<sup>35</sup>

### Hypocholesterolemic/hypolipidemic activity

The effect of consumption of germinated fenugreek seed powder on the blood lipid profiles of hypocholesterolemic adults was investigated. The outcomes of the study designated that consumption of the seed at both the levels resulted in a hypocholesterolemic effect. Between the two levels, higher levels of consumption, i.e., 18.0 gram of the germinated seed resulted in a significant reduction in total cholesterol and LDL levels.<sup>36</sup> The hypocholesterolemic and antioxidant activities of various extracts of fenugreek seeds were examined in cholesterol-fed rats. These results displayed that the ethyl acetate extract of the fenugreek seeds had a significant hypocholesterolemic effect and antioxidant activity in cholesterol-fed rats, whether this is somewhat due to the presence of flavonoids in the extract.<sup>37</sup> Effects of fenugreek on serum lipid profile in hypercholesteremic type 2 diabetic patients were studied. Administration of fenugreek seed powder caused significant reduction of serum total cholesterol, triacylglyceride and LDL-cholesterol in hypercholesteremic group. Whereas lipid profile in hypercholesteremic type 2 diabetic patients without fenugreek were not significant and fenugreek seed powder would be measured as effective agent for lipid lowering purposes.<sup>38</sup> The relationship between the lipid effects, the phenolic content, and the antioxidative effects of an ethyl acetate extract of fenugreek was investigated. Administration of fenugreek ethyl acetate extract meaningfully decreased the plasma levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol, while increasing the plasma level of high-density lipoprotein cholesterol. Also, the content of TBARS and catalase and superoxide dismutase activities in liver, heart and kidney decreased suggestively after oral administration

of the extract compared with those of rats fed a cholesterol-rich diet.<sup>39</sup> Hypolipidemic effect of fenugreek seeds and its comparison with atorvastatin on experimentally induced hyperlipidemia in rabbits was examined. Result of the study confirm that atorvastatin displayed a more potent hypolipidemic activity. It reduced serum total cholesterol, TG and VLDL cholesterol, and the atherogenic index highly significantly as compared to fenugreek.<sup>40</sup> Typolipidemic effect of fenugreek in hypercholesterolaemic patients was investigated. Result of the study demonstrated that there were no significant changes in lipid profile of group I received placebo 50 gm (rice powder and Bengal gram powder in equal measures) patients. In groups II -placebo 25 gm + FG 25 gm and Group III -FG 50 gm serum cholesterol, triglycerides and VLDL levels were significantly decreased when compared to group I.<sup>41</sup> Hypolipidemic effect of thermostable extract of fenugreek seeds was evaluated *in vitro* by engaging differentiating and differentiated 3T3-L1 cells, and HepG2 cells cultured in normal or sterol-enriched conditions. Results indicate that hypolipidemic effect of thermostable extract of fenugreek seeds is due to inhibition of fat accumulation as well as upregulation of LDLR. Taken together, the study suggests that thermostable extract of fenugreek seeds might have possible application in the managing of dyslipidemia and its related metabolic disorders.<sup>42</sup> Inhibitory effect of aqueous extract of *Trigonella foenum-graecum* seeds on fat accumulation and dyslipidemia in high fat diet- induced obese rats was investigated. Result showed that AqE-TFG treatment reduced the hepatic and cardiac thiobarbituric acid reactive substances and elevated the antioxidant enzyme levels. Moreover, liver and uterine WAT lipogenic enzyme and glucose-6-phosphate dehydrogenase activities were restored towards normal levels.<sup>43</sup>

### Anti-microbial activity

The silver nanoparticles of fenugreek seed showed antibacterial activities against both gram-negative and gram-positive bacteria. The ultrasound assisted nanoparticles showed higher stability and antibacterial and antioxidant activity compared with the nanoparticles fabricated by magnetic stirring.<sup>44</sup> The antimicrobial mechanisms and anticancer properties of the AgNPs synthesized using the seed extract of *Trigonella foenum-graecum* L was investigated. Result revealed that MIC of the AgNPs against *Aspergillus flavus*, *Trichophyton rubrum* and *Trichoderma viridiae* were each 250 µg mL<sup>-1</sup>, respectively. The extracellular protein concentration, levels of lactate dehydrogenase and alkaline phosphatase enzyme in the AgNPs treated bacterial pathogens demonstrated greater antimicrobial mechanism.<sup>45</sup> The antimicrobial activities of biosynthesized nanoparticles were examined through Kirby-Bauer method. The TF-TiO<sub>2</sub> nanoparticles exhibited substantial antimicrobial activity against all the tested microorganisms.<sup>46</sup>

### Anti-diabetic effect

A recent study result reported that administration of *Trigonella foenum-graecum* seed powder solution showed noticeable effects in improving lipid metabolism in type II diabetic patients. So, *Trigonella foenum-graecum* seed may deliver new alternatives for the clinical management of type II diabetes.<sup>47</sup> The effects of ethanol extract of Fenugreek seeds on the blood glucose levels in alloxan-induced diabetic rats were investigated. The hypoglycemic effect of extract was compared with that of the antidiabetic drug glimepiride, 4mg/kg single dose. The extract showed significant activity against the diabetic state induced by alloxan. The most effective dose recognized was 1g/kg but that is still lower than the standard antidiabetic drug.<sup>48</sup> A study was performed to evaluate the effects of supplementation with fenugreek seeds on plasma glucose and serum levels of cholesterol and insulin in alloxan-induced diabetic and in non-diabetic rabbits. Supplementation with fenugreek resulted in a significant decrease in glucose level of diabetic group of rabbits and a slight effect in non-diabetic

rabbits. Moreover, supplementation with fenugreek lowered the cholesterol level slightly in diabetic groups. The result established that antidiabetic and insulin mimetic effects of fenugreek seeds in rabbits.<sup>49</sup> The effect of oral feeding of *Trigonella foenum-graecum* seed powder (TSP) has been studied on blood glucose, monoamine oxidase, membrane fluidity, and glucose transporter-4 accumulation in the alloxan-induced diabetic rat brain was investigated. Result demonstrated that diabetic rats showed hyperglycemia with almost four-fold high blood glucose levels. Increased MAO activity with correlated increase in genomic DNA degradation in the diabetic brain supports the hypothesis that catecholamine oxidation is an important source of oxidative stress decreased of GLUT4 expression with diabetes in the brain. Overall study concluded that TSP exerts its anti-diabetic and neuroprotective effects, probably mediated through a decrease in hyperglycemia and oxidative stress thereby ameliorating the control and management of diabetic complications.<sup>50</sup>

### Nephroprotective effect

A study was performed on rats to evaluate the role of fenugreek on nephrotoxicity induced by aluminum chloride (AlCl<sub>3</sub>). Result revealed that treatment with the whole fenugreek seed powder (5% in the diet) showed its effectiveness in restoring normal plasma values of urea, creatinine, ALP and glucose, as well as re-increasing the TAS, inhibiting LPO and improving histopathological changes in the injured kidneys.<sup>51</sup> The nephroprotective efficacy of IND01 in animal model of diabetes with and without ischemia reperfusion injury was examined. Alloxan administration with or without ischemia reperfusion showed symptoms of severe nephropathy (decreased creatinine clearance, increased BUN, presence of glomerular matrix formation, tubular necrosis, interstitial inflammation as well as fibrosis. The daily oral administration of IND01 exhibited powerful and mild renoprotective effects on biochemical parameters against diabetic rats without ischemia (early nephropathy) and with ischemia model respectively. IND01 exhibited moderate protection from histological abnormalities in kidney of alloxan-induced rats without ischemia reperfusion injury.<sup>52</sup>

### Role of respiration

A study was performed to determine the efficiency of *Tregonella foenum graecum* (fenugreek) seeds in mild asthma. The participants were divided to three groups randomly. On group received fenugreek syrup one received honey syrup and the third got placebo. Duration of treatment was four weeks. Quality of life, Lung function tests and IL-4 levels were evaluated before and after treatment. After study there was substantial increase in quality of the life as well as lung function tests and IL-4 levels in fenugreek and honey groups. Moreover, FEV1 level was better more than 10% in fenugreek group. Treatment was well tolerated. No serious side effects were reported during the study.<sup>53</sup>

### Immunomodulatory effects

Immunomodulatory activity of aqueous extract of *Trigonella foenum graecum* L., was assessed in mice. Mice were treated with three doses of extract (50, 100 and 250 mg/kg body weight per os) for 10 days. At doses of 50 and 100 mg/kg, a significant increase in relative organ weight of thymus was noticed. As regards lymphoid organ cellularity, cellularities of thymus and bone marrow were significantly increased. *T. foenum graecum* extract elicited a significant ( $p < 0.001$ ) increase in the DTH response at doses of 50 and 100 mg/kg, Humoral immunity as measured by PFC showed an elevated response at a dose of 100 mg/kg, and in HT test, plant extract also showed modulatory effect at all the doses.<sup>54</sup> The immunomodulatory activity of ethanolic extract of Fenugreek was studied for phagocytic activity, cell mediated and humoral immune

system based on mice model. Fenugreek showed considerably high phagocytic index against control group, demonstrating stimulation of the reticulo-endothelial system. Substantial decrease in mean difference, in the foot paw thickness in DTH indicates its anti-inflammatory activity. In Fenugreek treated groups at 200 and 400 mg/kg doses showed significant increase in antibody titer whereas in T-cell population test, exhibited substantial increase in T-cell rosette formation against control.<sup>55</sup>

### Role in bone/osteoporosis

The effects of fenugreek seed on bone mechanical properties in rats with normal and decreased estrogen level (developing osteoporosis) was investigated. Result revealed that fenugreek seed added to food did not meaningfully affect bone mineralization and serum turnover markers, independently of the estrogen status. It inclined to increase the strength of the tibial metaphysis (cancellous bone) in non ovariectomized rats, and increased the strength of the femoral diaphysis (compact bone) in ovariectomized rats. Finally, study concluded that low dietary intake of fenugreek seed may cause slight favourable skeletal effects, while at high doses it might damage the skeletal system.<sup>56</sup> The role of dietary *Trigonella foenum graecum* seed extract on bone structure and mechanical properties in ovariectomized rats was examined. Result revealed that maximum flexor load to break femur bone was meaningfully low in ovariectomized rats in comparison with control rats. Supplementation with *Trigonella foenum graecum* pointedly improved the maximum flexor load and tibia dry weight compared to ovariectomized untreated rats. *Trigonella foenum graecum* administration also meaningfully conserved the trabecular and cortical bone thickness compared to ovariectomized rats. Overall, this finding advocates that dietary intake of *Trigonella foenum graecum* seeds can improve the bone structure and biomechanical properties in ovariectomized rats demonstrating that *Trigonella foenum graecum* may be an alternative treatment approach to prevent the menopause induced osteopenia.<sup>57</sup>

### Role in reproductive system

The effects of fenugreek seeds on the severity of primary dysmenorrhea among students was examined. Unmarried Students were arbitrarily allocated to two groups who got fenugreek or placebo. Result demonstrated that pain severity at baseline did not differ suggestively between the two groups. Pain severity was meaningfully reduced in both groups after the intervention; however, the fenugreek group experienced significantly larger pain reduction. Moreover, systemic symptoms of dysmenorrhea decreased in the fenugreek seed group. Overall, study concluded that prescription of fenugreek seed powder during menstruation can reduce the severity of dysmenorrhea.<sup>58</sup>

### Anti-cancer effect

Medicinal plants or their active compound has proven role in cancer inhibition and prevention.<sup>59-66</sup> Moreover, Medicinal plants or their chief ingredients confirms its role in cancer management through modulating various biological activities.<sup>67-72</sup> The extract from the seeds of fenugreek, are cytotoxic *in vitro* to a panel of cancer but not normal cells was examined. Treatment with 10-15 ug/mL of extract showed growth inhibitory to breast, pancreatic and prostate cancer cell lines. When tested at higher doses (15-20 ug/mL), extract continued to be growth inhibitory to PCa cell lines. Moreover, at least part of the growth inhibition is due to induction of cell death, as noticed by incorporation of Ethidium Bromide III into cancer cells exposed to extract.<sup>73</sup> The effect of diosgenin on breast cancer cell lines was examined. Cytotoxic assays revealed that diosgenin decreased the viability of both the ER positive MCF-7 cells and ER negative MDA 231 cells. A substantial induction of apoptosis by diosgenin was noticed in both the breast cancer cell lines. In MCF-7 cells diosgenin induced p53 protein expression and also down regulated ER activation.

Though, in MDA 231 cells diosgenin increased caspase activation and also down regulated Bcl-2 protein expression.<sup>74</sup> Another study based on osteosarcoma reported that diosgenin inhibits receptor-activated nuclear factor-kappaB ligand-induced osteoclastogenesis, suppresses tumor necrosis factor-induced invasion, and blocks the proliferation of tumor cells. Moreover, diosgenin suppressed TNF-induced NF-kappaB activation, activation of IkappaBalpha kinase, IkappaBalpha phosphorylation, IkappaBalpha degradation, p65 phosphorylation, and p65 nuclear translocation via inhibition of Akt activation. Finally, study propose that diosgenin suppresses proliferation, inhibits invasion, and suppresses osteoclastogenesis *via* inhibition of NF-kappaB-regulated gene expression and enhances apoptosis.<sup>4</sup> Another study based on a mouse xenograft model reported that a combination of Thymoquinone (TQ) and diosgenin (DG) meaningfully reduced tumor volume, mass as well as increased apoptosis. Thymoquinone (TQ) and diosgenin (DG), alone and in combination, inhibit cell proliferation as well as induce apoptosis in squamous cell carcinoma. The combination of Thymoquinone (TQ) and diosgenin (DG) is a potential antineoplastic therapy in this common skin cancer.<sup>5</sup> The effect of diosgenin on TRAIL-induced apoptosis in colorectal cancer cell lines was examined. It was reported that diosgenin sensitizes colorectal cancer cell lines HT-29 cells to TRAIL-induced apoptosis. Mechanisms primary this sensitization mostly involved diosgenin-induced p38 MAPK pathway activation and subsequent DR5 overexpression. Additionally, it was confirmed that diosgenin alone, TRAIL alone or combination treatment increased cyclooxygenase-2 expression and that the use of a cyclooxygenase-2 inhibitor further increased apoptosis induction.<sup>75</sup> Anti-cancer activity of diosgenin and its mechanisms in chronic myeloid leukemia (CML) cells. Diosgenin-induced autophagy and cytotoxicity were conveyed by reactive oxygen species generation and mammalian target of rapamycin signaling pathway inhibition. Result confirmed that diosgenin clearly generates reactive oxygen species and this oxidative pressure not only produces cytotoxic effect on chronic myeloid leukemia cells and induces autophagy.<sup>76</sup> The preventive effectiveness of fenugreek seed and its major constituent, diosgenin, on azoxymethane-induced rat colon carcinogenesis during initiation and promotion stages was investigated. Dietary FSP at 1% and diosgenin at 0.1% fed only during the promotional stage also inhibited total ACF up to 33%. Additionally, diosgenin induced apoptosis in HT-29 cells at least in part by inhibition of bcl-2 and via induction of caspase-3 protein expression.<sup>77</sup> The impact of diosgenin on the human mammary carcinoma cell line and to examine its therapeutic potential against *N*-nitroso-*N*-methylurea-induced experimental breast cancer. In *in vitro* studies, diosgenin significantly inhibited the proliferation of MCF-7 cells in a dose-dependent manner and. Elevated lipid peroxidation in *N*-nitroso-*N*-methylurea-induced breast cancer-bearing animals were drim down due to management with steroidal diosgenin.. From the finding, it was reported that diosgenin may be used as a chemoprotective agent against human mammary carcinoma.<sup>78</sup> The anticancer properties and proteomic profiles of fenugreek seeds, and is encouraged by the clinical profile of a case of primary CNS T cell lymphoma that countered to fenugreek treatment and resulted in tumor regression. It was noticed that selective cytotoxic effects of fenugreek extract *in vitro* to a panel of cancer cell lines, including T-cell lymphoma. Overall, *in vitro* effect of fenugreek as a substance with significant cytotoxicity to cancer cells points to the potential usefulness of fenugreek in the prevention and treatment of cancer.<sup>79</sup> Crude methanol extract of Fenugreek seeds was prepared and its anticancer mechanism was assessed, through HepG2 cell line. Result confirmed that extract treatment showed a cytotoxic effect and apoptosis induction in a dose-dependent manner that was arbitrated by upregulation of p53, Bax, PCNA, and caspase-3 activation in HepG2 cells. Overall, extract act as a promising nontoxic herbal with therapeutic potential to induce apoptosis in HepG2 cells via p53, Bax, and PCNA upregulation in caspase-3 dependent manner.<sup>80</sup>

## CONCLUSION

Fenugreek is a plant of family fabaceae and it is used as a dietary supplement and very useful in the management of various diseases through its antioxidant, anti-inflammatory, hepatoprotective, cardioprotective, neuroprotective, immunomodulatory, nephroprotective and antimicrobial activity. Moreover, fenugreek seed are rich sources of various essential compounds and these components play a significant role in the inhibition and prevention of various cancers. In this context, the present study aims to provide an extensive overview to fenugreek therapeutic implication in human subjects. Detailed study based on clinical trials should be warranted to explore the role of fenugreek in the management of various diseases.

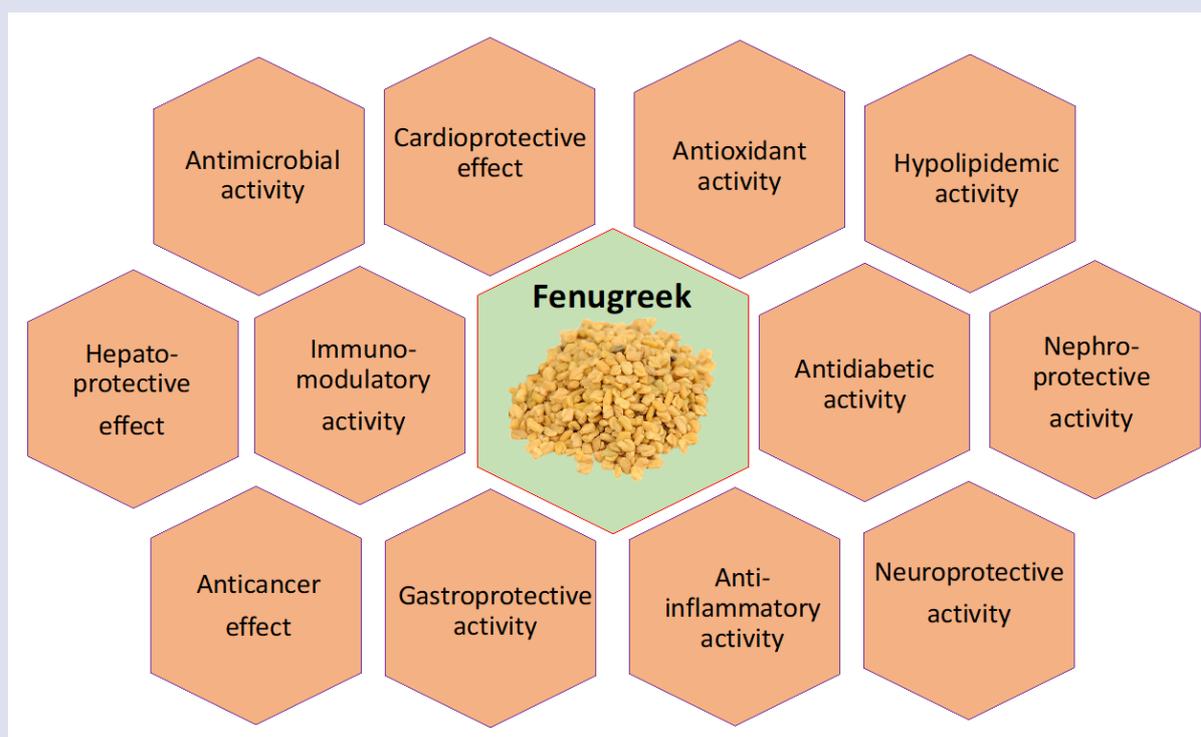
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## GRAPHICAL ABSTRACT



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