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Pomegranate alleviates metabolic syndrome: A Systematic review

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Abstract
Currently the role of fruit as dietary supplement and as a prophylactic therapeutic agent in treating chronic degenerative long term illness is gaining interest. Pomegranate (*Punica granatum* L.) is a nutritious dense fruit that imparts several health benefits. Various parts of pomegranate such as the fruit, seed, stem, peel, rind and leaves contains bioactive constituents that are reported to possess medicinal and therapeutic properties. The information pertaining to this review article was obtained from accessible journals in several databases such as Web of Science, PubMed, Scopus and Embase. The search terms used were "pomegranate" and "*punica granatum*". Result of several scientific research studies highlights the role of pomegranate in treating chronic diseases such as diabetes, blood pressure and cardiovascular diseases. Though the present review article clearly portrays the medicinal properties of pomegranate, further and more research is necessary to exploit and unravel other useful and unknown medicinal properties of pomegranate.

Keywords: Pomegranate, medicinal properties, dietary supplement

Introduction
Pomegranate (*Punica granatum* L.), derived from the Latin word pomum "apple" and granatum "seeded" is an edible fruit cultivated in many countries and is consumed around the world. India is a native land of the pomegranate which is grown both coastal and mountainous areas [1]. The total pomegranate production in India was 665,000 tons in 2005. The pomegranate tree typically grows 12-16 feet, has many spiny branches, and can be extremely long lived. The leaves are glossy and lance shaped, and the bark of the tree turns gray as the tree ages. The flowers are large, red, white, or variegated and have a tubular calyx that eventually becomes the fruit. The ripe pomegranate fruit can be up to five inches wide with a deep red, leathery skin, is grenade-shaped, and crowned by the pointed calyx. The fruit contains many seeds (arils) separated by white, membranous pericarp, and each is surrounded by small amounts of tart, red juice. Seeds are a rich source of dietary fiber.

Scientific Classification

Kingdom	-	Plantae
Division	-	Magnoliophyta
Class	-	Magnoliopsida
Order	-	Myrtales
Family	-	Punicaceae
Genus	-	*Punica*
Species	-	*granatum*

Fig 1: A) whole fruit, B) Longitudinal section with numerous arils, C) closer view of open fruit packed with arils, D) Whole arils and cleaned seeds with juice and pulp removed.

Constituents of pomegranate

Pomegranate which is consumed either as fresh fruit or in other forms like juice, jams and jellies contains several bioactive constituents that contributes to many medicinal properties such as antioxidant, anticancer, hypolipidemic, hypoglycemic and antimicrobial activity [2]. Edible parts of pomegranate fruit (about 50% of the total fruit weight) comprise 80% juice and 20% seeds. The synergistic action of the pomegranate constituents appears to be superior to that of single constituents. Principle constituents of pomegranate fruit parts are presented in table 1. The presence of significant amounts of bioactive compounds, such as phenolic acids, flavonoids, and tannins in pomegranate fruits assures them considerable nutritional value and therapeutic activities [3]. The nutritive value of pomegranate fruit is given in table 2.

Table 1: Principle constituents of Pomegranate Fruit Parts

Plant components	Constituents
Juice	Fresh juice contains 85% water, 10% total sugars, and 1.5% pectin, ascorbic acid, calcium is 50% of its ash content; and the principal amino acids are glutamic and aspartic acids, numerous minerals, particularly iron [3, 4, 5] anthocyanins, especially the 3-glucosides and 3, 5- diglucosides of delphinidin, cyanidin, and pelargonidin [6] ellagic acid, gallic acid, caffeic acid [7] with gallagyl-type tannins, ellagic acid derivatives, other hydrolysable tannins, and polyphenolic flavonoids (quercetin, kaempferol, and luteolin glycosides) [8, 9, 10, 11] catechin, Epigallocatechin gallate (EGCG) and rutin [12, 13].
Seed	Pomegranate seed oil consists of about 80% conjugated octadecatrienoic fatty acids, with a high content of 9-cis, 11-trans, 13-cisacid or punicic acid (PA), one of the isomers of conjugated linolenic acid (CLN) including ellagic acid sterols and other fatty acids [7, 14, 15, 16]. Dried pomegranate seeds contain the steroid estrogen estrone [17, 18] the isoflavone phytoestrogens genistein and daidzein, and the phytoestrogen coumestrol [19]. Pomegranate seeds are a rich source of crude fibers, pectin, and sugars.
Pericarp (husk, peel, rind)	Phenolic punicalagins; gallic acid and other fatty acids [7] catechin, EGCG [13] quercetin, rutin, and other flavonols [12] flavones, flavonones [20, 21].
Leaves	Tannins (punicalin and punicafolin); and flavone glycosides, Including luteolinand apigenin [20].
Flower	Gallic acid, ursolic acid [22] triterpenoids, including maslinic, asiatic acid; oleanolic acid [23].
Roots and bark	Ellagitannins, including punicalin, punicalagin and numerous piperidine alkaloids [24, 25].

Table 2: Nutritive value of pomegranate

Nutrients	Units	Value per 100 grams
Proximate		
Water	G	77.93
Energy	Kcal	83
Protein	G	1.67
Total lipid (fat)	G	1.17
Carbohydrate	G	18.70
Dietary Fiber	G	4.0
Sugars, total	G	13.67
Minerals		
Calcium	Mg	10
Iron	Mg	0.30
Magnesium	Mg	12
Phosphorus	Mg	36
Potassium	Mg	236
Sodium	Mg	3
Zinc	Mg	0.35
Copper	Mg	0.158
Manganese	Mg	0.119
Selenium	µg	0.5
Vitamins		
Vitamin C	Mg	10.2
Thiamin	Mg	0.067
Riboflavin	Mg	0.053
Niacin	Mg	0.293
Pantothenic acid	Mg	0.377
Vitamin B_6	Mg	0.075
Folate	µg	38
Choline	Mg	7.6
Vitamin B_{12}	µg	0.00
Vitamin A, RAE	mcg_RAE	0
Vitamin E (alpha-tocopherol)	Mg	0.60
Vitamin D	IU	0
Vitamin K (phylloquinone)	µg	16.4

Phytochemistry of Pomegranate

Phytochemicals are secondary metabolites produced by plants as a defense mechanism against various stressors such as harmful ultraviolet radiation, pathogens and herbivorous predators. Epidemiological studies suggests that the consumption of a plant-based or phytochemical-rich diet can promote general health and reduces the risk of chronic degenerative conditions such as certain types of cancers, inflammation, cardiovascular and neurodegenerative diseases [26, 27, 28]. All the parts of pomegranate are of therapeutic importance due the abundance of bioactive constituents in them. The major class of phytochemicals present in pomegranate is polyphenols. Preliminary phytochemical screening in fruit, peel, flower and leaf indicated the presence of phenolics, flavonoids, coumarins, tannins, terpenoids, alkaloids, saponins, phycobilins [29, 30]. The presence or absence of a phytochemical may vary according to the type of pomegranate cultivar analysed. The quantification of the phytochemicals and components isolated from different part of the pomegranate fruit and plant are discussed below.

Pomegranate Juice

One of the important product of pomegranate fruit is obtained either from arils or whole fruit. [31] Pomegranate juice is a generally rich in sugars such as fructose, sucrose, and glucose; and organic acids such as ascorbic acid, citric acid, fumaric acid, and malic acid [32]. Hmid *et al*. [33] quantified phenolic and flavonoid compounds of 18 cultivars of pomegranates in Morocco. The phenol and flavonoids content of juices from 18 cultivars of pomegranates varied from 1385 to 9476 mg GAE/L and 14,446 to 56989 mg RE/L of juice respectively. Further HPLC analysis of juices identified 10 phenolic compounds which were hydroxybenzoic acids such as gallic and ellagic acids, hydroxycinnamic acids such as

chlorogenic, caffeic and ferulic acids, flavan-3-ols such as catechin and epicatechin, dihydrochalcones such as phloridzin, flavonols such as quercetin and flavonol, glycosides such as rutin.

Pomegranate seed

The dried seeds of the pomegranate fruit are used as a culinary spice and are rich source of dietary fibre [34, 35]. The quantitative phytochemical analysis of the pomegranate seed extract revealed that flavonoid content was highest (121.22 mg/g); followed by phenol (78.12 mg/g), saponins (12.87%), tannins (3.30 mg/g) and alkaloid (1.51 mg/g) [36]. The major fatty acid found in pomegranate seed is punicic acid (71.2 to 77.6 %) followed by oleic acid (7.6 to 9.1%) and linoleic acid (7.47 to 8.82%). The ɣ- tocopherolcontent of the seed varied from 236 mg/100 g to 389 mg/100 g [37].

Pomegranate Peel

Peels of the fruit are popularly used among folk medicine practioner because of its strong astringency. Phytochemical analysis of pomegranate peels carried out by Ambigaipalan *et al*., [38] using HPLC–DAD–ESI/MS (high-performance liquid chromatography coupled to photodiode array detector and mass spectrometer) detected Proanthocyanidines, gallic acid, kaempferol 3-O-glucoside, ellagic acid and monogalloyl-hexoside were the major procyanidin dimers. While the HPLC analysis of peel juice conducted by Farag *et al*., [39] reported 30 components, the major components being gallic acid (14.15%) and protocatechuic acid (14.51%). The total phenol and flavonoid content of peel was found to be 58.63±0.129 mg GAE/g dryweight and 47.32±0.032mg QE/g dry weight.

Pomegranate flower and leaves

The phenolic content of the pomegranate flower ranges from 15.19±2.02 to 25.94±7.00 mg GAE/g dry weight depending on the cultivar of pomegranate studied. While the total flavonoid and total tannin content of the flower varies from 11.46±2.17 – 23.06±3.46 mg QE/g dry weight and 1.06±0.11 – 2.03±0.15 % respectively [40]. The total phenol and flavonoid content of leaves was found to be 48.02±0.12 mg GAE/g dryweight and 33.02±0.009 mg QE/g dry weight [39]. The major phtyochemicals are presented in Fig 2

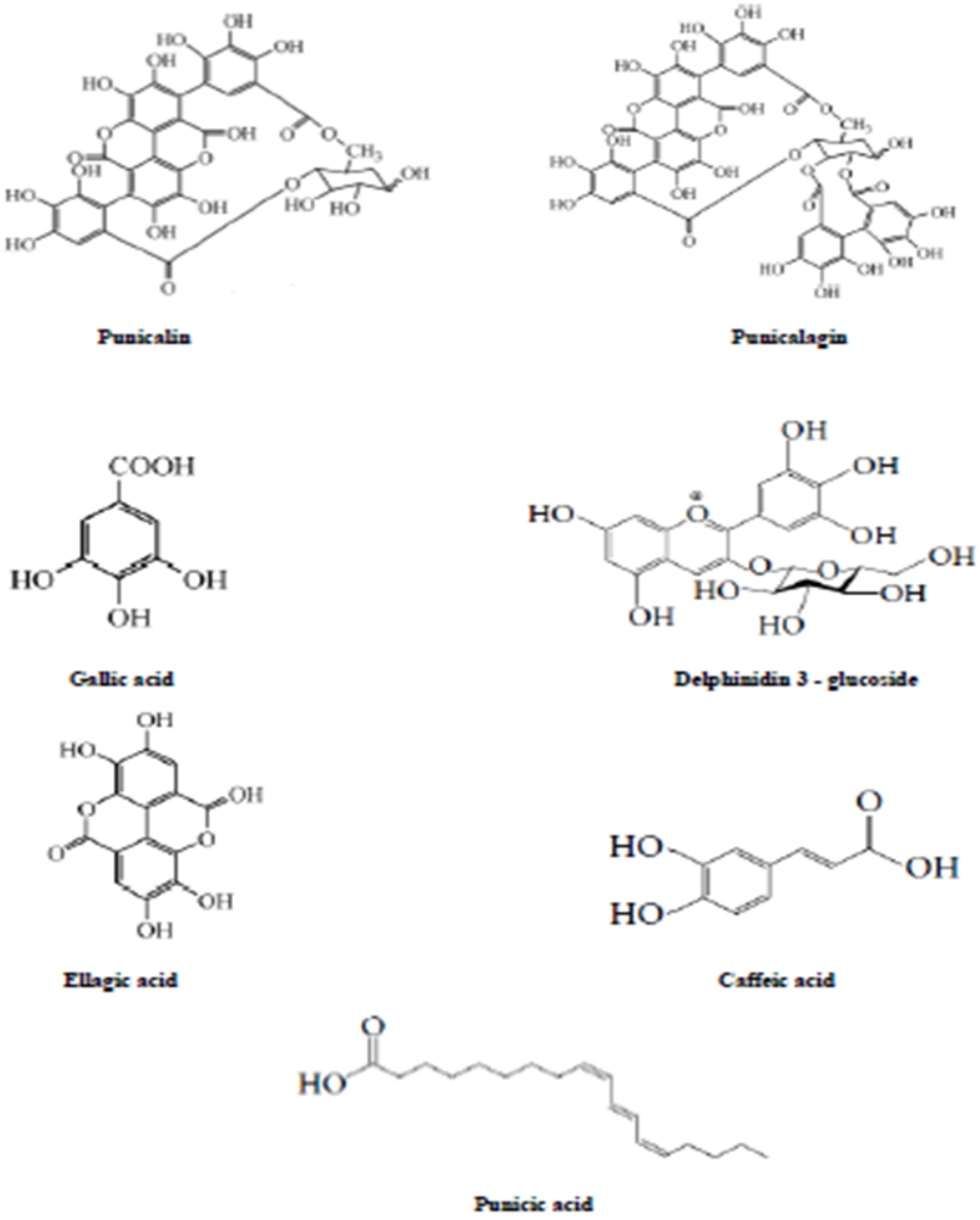

Fig 2: The major phtyochemicals are presented

Pomegranate - antioxidant agent

All the biological systems in the body are under constant and continuous influence of oxidative stress due to excess production of free radicals. Free radicals or reactive oxygen species (ROS) are produced in the body when cells use oxygen to generate energy from cellular redox process [41]. These free radicals occupy a key role in the etiology of several chronic illness such as cancer and atherosclerosis as they damage biomolecules such as DNA, proteins and lipids [42]. Antioxidants are compounds that interact, stabilize and protect cells from damage caused by free radicals. Antioxidants present in nature may be either exogenous or endogenous. The endogenous antioxidants can be classified as enzymatic and non-enzymatic. The non-enzymatic antioxidants are also divided into metabolic antioxidants and nutrient antioxidants. There has been a global shift toward the use of natural substance present in medicinal plants as therapeutic antioxidants due to the inverse relationship between the dietary intake of antioxidant-rich foods and incidence of human diseases. Pomegranate contains phytonutrients such as polyphenols, tannins, anthocyanins, along with other essential micronutrients such as vitamin C, vitamin E and lipoic acid. Anthocyanins and derivatives of ellagic acid present in pomegranate accounts for antioxidant activity [43]. Results of several *in vitro* free radical scavenging and reducing power assays provides substantial evidence that pomegranate is rich in antioxidants.

The antioxidant activity of pomegranate juice was evaluated by four different methods (ABTS, DPPH, DMPD, and FRAP) and compared to those of red wine and a green tea infusion. Commercial pomegranate juice showed an antioxidant activity (18−20 TEAC) three times higher than those of red wine and green tea (6−8 TEAC). HPLC-DAD and HPLC-MS analyses of the juice revealed that commercial juice contained the pomegranate tannin punicalagin (1500−1900 mg/L). This could account for the high antioxidant activity of commercial juices compared to the experimental ones. In addition, anthocyanins, ellagic acid derivatives, and hydrolyzable tannins were detected and quantified in the pomegranate juices [9]. Another study conducted by Elfalleh *et al*., [44] found that free radical scavenging is about 3.58±0.38 µg/mL in pomegranate peel. The antioxidant capacity value determined by ABTS was 7.364 ± 0.403 mMTrolox equivalent antioxidant capacity/100 g dry weight. These findings implied that bio-active compounds from the peel and juice might be potential resources for the development of antioxidant function dietary food.

Louis *et al*., [45] studied the effect of pomegranate juice, for its capacity to protect nitric oxide (NO) against oxidative destruction and enhance the biological actions of nitric oxide. Pomegranate juice was found to be a potent inhibitor of superoxide anion-mediated disappearance of nitric oxide. Pomegranate juice was much more potent than Concord grape juice, blueberry juice, red wine, ascorbic acid, and dl-α-tocopherol. As little as 3 µL of a 6-fold dilution of pomegranate juice, in a reaction volume of 5000 µL, produced a marked antioxidant effect, whereas 300 µL of undiluted blueberry juice or nearly 1000 µL of undiluted Concord grape juice were required to produce similar effects. Pomegranate juice and other antioxidant-containing products were found to augment the anti-proliferative action of nitric oxide on vascular smooth muscle cell (rat aorta) proliferation. Similarly, Ignarro *et al*., [46] also reported that pomegranate juice prevents oxidative destruction of nitric oxide. The authors also stated that pomegranate juice has significantly greater antioxidant capacity at lower concentrations. The antioxidant activity of juice, arils and rind extract of pomegranate was evaluated by Ricci *et al*. [47] using DPPH and lipo oxygenase assay respectively. Results showed all the three parts of pomegranate fruit exhibited greater antioxidant activity.

Teresa *et al*., [48] studied the *in vitro* effects of treatment with either pomegranate juice (PJ) or with polyphenol-rich extract obtained from pomegranate fruit on platelet aggregation, calcium mobilization, thromboxaneA2 production, and hydrogen peroxide formation, induced by collagen and arachidonic acid. Pomegranate juice and pomegranate fruit reduce all the platelet responses studied. The pomegranate fruit showed a stronger action in reducing platelet activation. These results demonstrated that the cardiovascular health benefits of pomegranate may in part be related to the ability of polyphenols to inhibit platelet function. In fact, pomegranate juice and pomegranate extract have similar effects at concentrations expected for normal intake.

Pomegranate contains several phenolic compounds that can scavenge the free radicals produced in the body. Gallic acid, ellagic acid and punicalagin (a tannin polyphenolic compound) present in the husk of pomegranate is known for its anti-proliferative and anti – inflammatory action [49]. Anthocyanins such as delphinidin, cyanidin and pelargonidin present in pomegranate juice exhibits antioxidant activity [50, 51]. Aloqbi *et al*. [52] compared the antioxidant potential of punicalagin and pomegranate juice. The results showed that pomegranate juice significantly inhibited the action of free radicals namely DPPH and hydrogen peroxide while punicalagin exhibited greater reducing power ability that increased with increase in concentration ($p<0.01$).

Imbalance between free radicals and antioxidant status is termed as oxidative stress. Oxidative stress contributes to cardiovascular diseases, diabetes mellitus and cancer by several pathways namely by inducing lipid peroxidation, activation of platelets and proliferation of vascular smooth muscle cells [53]. Among the *in vivo* experiments aimed at evaluating the biological effects of pomegranate juice, Aviram *et al*. [3] tested the effect of pomegranate juice consumption in healthy male and atherosclerotic, apolipoprotein E-deficient mice. The authors demonstrated that the supplement has antiatherogenic properties with respect to all three related components of atheroscelerosis: it significantly affected plasma lipoproteins, arterial macrophages and blood platelets, all of which attributed to the antioxidant effects specially ellagitannins. A pilot study conducted by Esmaillzadeh [54] in type 2 diabetic patients with hyperlipidemia found that concentrated pomegranate juice decreased cholesterol absorption, increased fecal excretion of cholesterol, had a beneficial effect on enzymes involved in cholesterol metabolism, significantly reduced total and LDL cholesterol, and improved total/HDL and LDL/HDL cholesterol ratios. It can be concluded that concentrated pomegranate juice consumption may modify heart disease risk factors in hyperlipidemic patients, and its inclusion therefore in their diets may be beneficial.

Kishore *et al*. [55] reported the protective effect of pomegranate fruit extract against Adriamycin induced oxidative stress in chick embryo model at a dosage of 200 µg/egg. In addition, the study also demonstrated that the antioxidant power of pomegranate was greater than red wine and green tea. Cambay *et al*. [56] also proved that supplementing juice extract obtained from pomegranate flower reduced oxidative stress among diabetic rats. Balbir *et*

al. [57] reported that supplementing pomegranate juice to subjects with rheumatoid arthritis was instrumental in decreasing lipid peroxidation by 25% caused by free radicals. Groundbreaking research has been conducted to prove the anti-atherogenic, anti-diabetic and anti-hypertensive action of pomegranates. Clinical applications of pomegranate juice supplementation with special reference to metabolic syndrome are presented in table 3.

Table 3: Clinical applications of pomegranate juice supplementation with special reference to metabolic syndrome

Reference	Population	Duration And amount of supplementation	Results
Aviram *et al*., (2000) [3].	13 healthy, nonsmoking men aged 20–35 y (Lipid Research Laboratory, Israel)	50mL/day For 2 weeks	LDL susceptibility to aggregation and retention and increase in the activity of serum paraoxonase (HDL associated esterase) by 20%. No significant effect on the plasma lipid profile.
Esmaillzadeh *et al*., (2004) [54].	22 type II diabetic patients (14 women and 8 men) with hyperlipidemia (Iranian Diabetes Society)	40g/day For 8 weeks	Significant reduction in total cholesterol (from 202.4±27.7 mg/dL at baseline to 191.4±21 mg/dL at study conclusion), LDL (124.4±31.9 mg/dL at baseline to 112.9±25.9 mg/dL at study conclusion), LDL/HDL (3.4±1.2 at baseline to 3.0±0.9 at study conclusion) and total cholesterol/HDL (5.5±1.3 at baseline to 5.1±1.1 at study conclusion). No significant changes in serum triacylglycerol and HDL cholesterol
Aviram *et al*., (2004) [58].	10 patients with carotid artery stenosis (ages 62-77; seven men and three women)	50mL/day For 1 year	Significant reduction (30%) in carotid intima-media thickness, serum LDL basal oxidative state (90%), LDL susceptibility to copper ion-induced oxidation (59%), and serum levels of antibodies against oxidized LDL (19%). Significant increases in serum paraoxonase1 activity (83%) and serum total antioxidant status (130%). Seven of 10 subjects experienced a 36% average decrease in serum ACE activity and a small, but significant, five-percent decrease in systolic blood pressure (21%).
			No additional beneficial effects on carotid intima-media thickness serum paraoxonase1 activity. 16% reduction in serum lipid peroxidation
Sumner *et al*., (2005) [59].	45 patients with myocardial ischemic coronary heart diseases (The Preventive Medicine Research Institute, California)	240mL/day For 3 months	Reduction in stress-induced ischemia ($p>0.05$).
Rosenblat *et al*., (2006) [60].	10 male healthy subjects (controls) and 10 male Type II diabetes patients (35–71 years old) (Lipid Research Laboratory, Israel)	50mL/day For 3 months	Supplement did not affect serum glucose, cholesterol and triglyceride levels, but it resulted in a significant reduction in serum lipid peroxides (56%), thiobarbituric acid reactive substances levels (28%), cellular peroxides (71%), OxLDL cellular uptake (39%) and serum C-peptide values (23%). Significant increase in serum thiols (12%), paraoxonase1 activity (24%), and glutathione levels (141%).
Davidson *et al*., (2009) [61].	Experimental group (n = 146) and a control group (n =143) Men and women (45 to 74 years old) with ≥1 major CHD risk factor and baseline posterior wall carotid intima–media thickness 0.7 to 2.0 mm, without significant stenosis (Lipid Research Laboratory, Israel)	240mL/day for18 months	Pomegranate juice consumption had no significant effect on overall carotid intima–media thickness progression rate but significantly lessen the anterior wall and/or composite carotid intima–media thickness progression in subjects with increased oxidative stress and disturbances in the TG-rich lipoprotein/HDL axis
Hashemi *et al*., (2010) [62].	Randomized controlled clinical trial was conducted among 30 adolescents, aged 12–15 years, with metabolic syndrome. (Isfahan University of Medical Sciences, Iran)	240mL/day For 1 month	No significant change in BMI after trial, Flow-mediated dilation at 90 seconds and after nitroglycerin improved significantly within 4 hours of drinking juice. Daily consumption of diets rich in antioxidants might improve endothelial function in adolescents with metabolic syndrome.

Conclusion

The above findings thereby confirm the usage of pomegranate in treating several chronic illnesses. Pomegranate exerts biological functions through various ways by acting as a strong antioxidant agent, reducing inflammation and also decreases the plasma concentration of lipoproteins and formation of atherosclerotic lesions. In addition, more research needs to be carried to isolate other active compounds present in pomegranate and its role in curing other disorders using *in vitro* and *in vivo* studies.

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