



# ‘Magnesium’-the master cation-as a drug—possibilities and evidences

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**Abstract** Magnesium ( $Mg^{2+}$ ) is the 2nd most abundant intracellular cation, which participates in various enzymatic reactions; there by regulating vital biological functions. Magnesium ( $Mg^{2+}$ ) can regulate several cations, including sodium, potassium, and calcium; it consequently maintains physiological functions like impulse conduction, blood pressure, heart rhythm, and muscle contraction. But, it doesn't get much attention in account with its functions, making it a “Forgotten cation”. Like other cations, maintenance of the normal physiological level of  $Mg^{2+}$  is important. Its deficiency is associated with various diseases, which point out to the importance of  $Mg^{2+}$  as a drug. The roles of  $Mg^{2+}$  such as natural calcium antagonist, glutamate NMDA receptor blocker, vasodilator, antioxidant and anti-inflammatory agent are responsible for its therapeutic benefits. Various salts of  $Mg^{2+}$  are currently in clinical use, but their application is limited. This review collates all the possible mechanisms behind the behavior of magnesium as a drug at different disease conditions with clinical shreds of evidence.

**Keywords** Magnesium · Calcium antagonist · Hypomagnesemia · NMDA blocker · Forgotten cation · Vasodilator

## Abbreviations

ACE	Angiotensin converting enzyme
AD	Alzheimer's disease (AD)
ALP	Alkaline phosphatase
ALT	Aminotransferase
AMPA	$\alpha$ -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APP	Amyloid precursor protein
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BBB	Blood brain barrier
BMD	Bone mineral density
BMP2	Bone morphogenetic protein 2
BP	Blood pressure
cAMP	Cyclic Adenosine mono phosphate
CAD	Coronary artery diseases
CFTR	Cystic fibrosis transmembrane conductance regulator
CGRP	Calcitonin gene related peptide
CHF	Congestive heart Failure
Claudin	CLDN
CNS	Central nervous system
CSD	Cortical spreading depression
CSF	Cerebrospinal fluid
CTF $\beta$	C terminal fragment $\beta$
CVD	Cardiovascular diseases

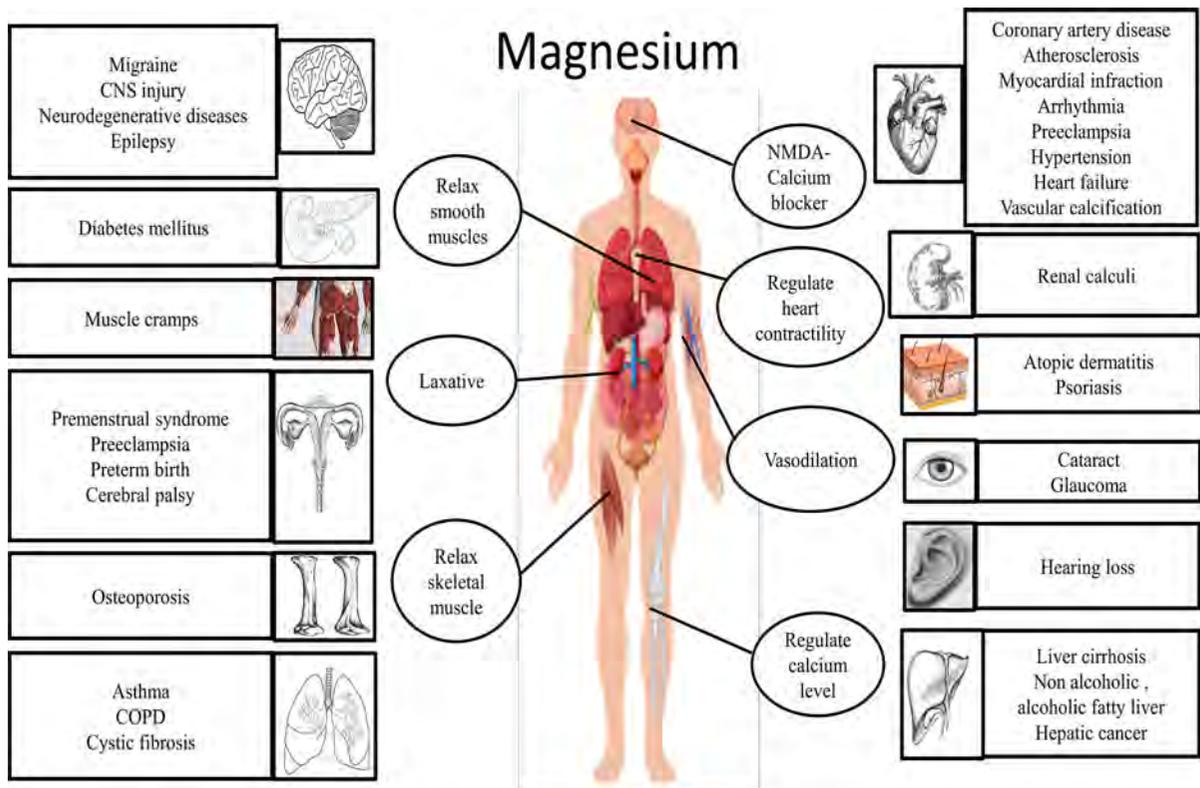
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DRE	Drug resistant epilepsy	SLC41	Solute Carrier Family transporter
ECF	Extracellular fluid	SOD	Superoxide dismutase
ECG	Electrocardiogram	TAL	Thick ascending limb of the Loop of Henle
EGF	Epidermal growth factor	TGF- $\beta$	Transforming Growth Factor- $\beta$
EMT	Epithelial-mesenchymal transition	TLRT-2	Toll-like receptor type-2().
GABA	Gamma amino butyric acid	TNF $\alpha$	Tumor necrosis factor alpha
GABA <sub>A</sub>	Gamma amino butyric acid receptor A	VEGF	Vascular endothelial growth factor
GLUT-1	Glucose transporter 1	WHO	World Health Organisation
GSK-3 $\beta$	Glycogen synthase kinase-3 $\beta$	XMEN-	Barr virus infection and neoplasia (XMEN)
HbA1	Haemoglobin, alpha 1	Epstein	
HBV	Hepatitis B virus infection	$\alpha$ -SMA	$\alpha$ -Smooth muscle actin
HCC	Hepatic cellular carcinoma		
HSC	Hepatic stellate cells		
IL 1	Interleukin 1		
IMT	Carotid Intima-Media Thickness		
LDLR	Low-density lipoprotein receptor LDLR		
MagT1	Magnesium transporter 1		
MAPK	Mitogen-activated protein kinase		
MEP	Maximal expiratory pressure		
Mg <sup>2+</sup>	Magnesium		
MI	Myocardial infarction		
MIP	Maximal Inspiratory Pressure		
Mrs2	Mitochondrial RNA splicing 2		
Mtor	Mammalian target of rapamycin		
Na <sup>+</sup>	Sodium		
NAFLD	Non-alcoholic fatty liver diseases		
NF- $\kappa$ B	Nuclear factor kappa light chain enhancer of activated B cells		
NMDA-N	Methyl D aspartate		
NO	Nitric oxide		
PEG	Polyethylene glycol		
PGF	Placental growth factor		
Pi	Inorganic phosphate		
PKC $\epsilon$	Protein kinase C epsilon type		
PLC $\gamma$ 1	Phosphoinositide phospholipase C		
PPAR- $\gamma$	Peroxisome proliferator- activated receptor gamma		
PUFA	Polyunsaturated Fatty Acids		
PD	Parkinson's disease		
RBC	Red blood cells		
DCT	Distal convoluted tubule		
RDA	Recommended daily allowance dose		
TRPM	Transient receptor potential channel for melastatin		
RNA	Ribonucleic acid		
ROS	Reactive oxygen species		
RUNX2	Runt-related transcription factor 2		

## Introduction

Macrominerals play important roles in regulating various vital functions in the human body and reducing risks for getting chronic diseases. Macroelements include elements such as calcium, magnesium, and phosphorous (Chronic et al. 1990). Magnesium (Mg<sup>2+</sup>) is an important **divalent element** belonging to the alkaline earth metal group. Magnesium is regarded as the **4th most abundant element in the body** and the **2nd most intracellular cation (Romani 2011b; Jahnen-Dechent and Ketteler 2012)**. It plays various roles, such as acting as a cofactor for more than 300 enzymes, regulating physiological functioning of the heart and neurons, regulating blood pressure (BP), blood sugar level, etc. **Besides, it also acts as a signaling molecule, reduces the neuronal excitotoxicity, maintains the level of potassium and calcium, regulates the synthesis, storage, and transport of ATP (Adenosine triphosphate) (McLean 1994; Rude 1989; Bharadwaj et al. 2014; Pham et al. 2014)**. Overall, magnesium (Mg<sup>2+</sup>) is considered as an important cation for maintaining normal physiological functions, as shown in Fig. 1 (Rude 1989; de Baaij et al. 2015; Pham et al. 2014). **But magnesium (Mg<sup>2+</sup>) doesn't get much attention due to two reasons**. The first reason is that symptoms associated with altered Mg<sup>2+</sup> levels appear only **when the level becomes too low or too high**. The second reason is that its exact role in maintaining normal physiology is **poorly understood**, making it a "forgotten cation." (Bharadwaj et al. 2014; Ahmed and Mohammed 2019).

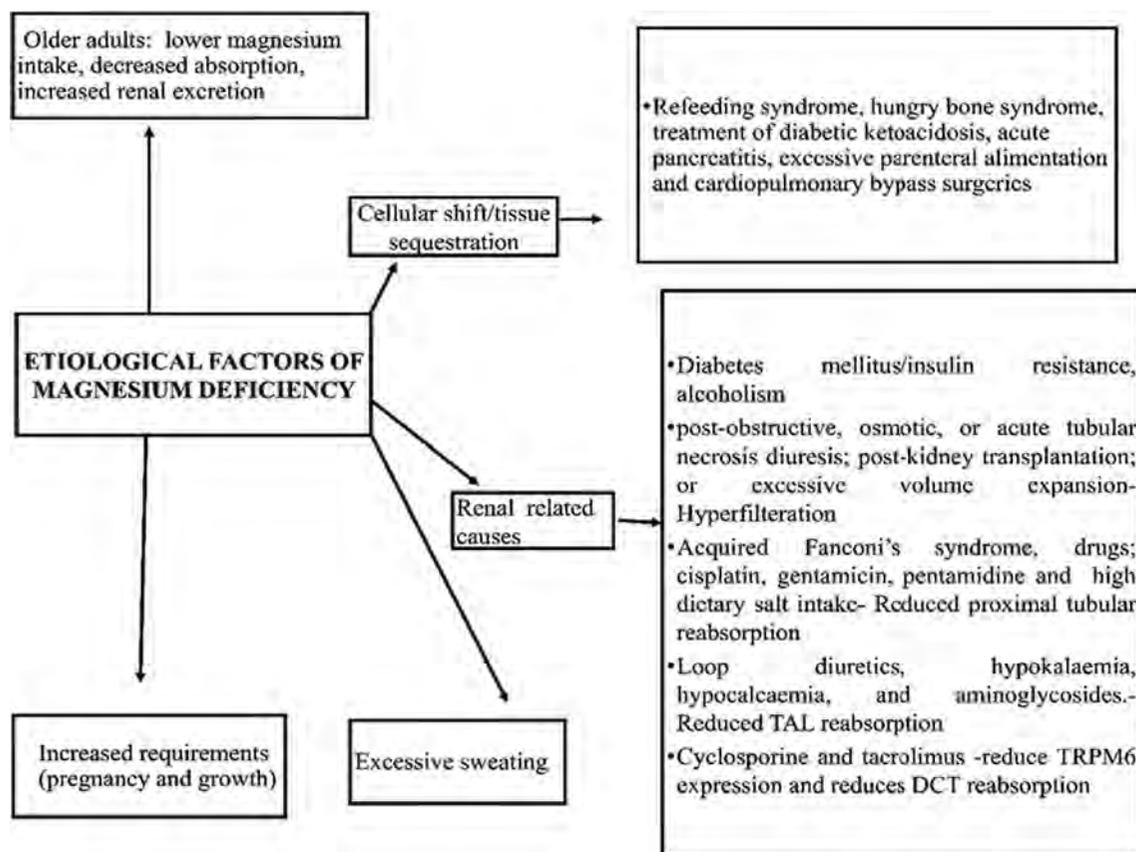
K+ =  
1st



**Fig. 1** Physiological roles of magnesium on vital systems. Text in the circle represents the physiological role of Mg in various vital organs. Text in the rectangle indicate the diseases or disorders associated with magnesium deficiency

As per the United States Food and Nutrition, Recommended Daily Allowance (RDA) of  $Mg^{2+}$  is 420 mg for males and 320 mg for females. Around 10% of it is obtained through drinking water. Other sources of  $Mg^{2+}$  include green vegetables, unprocessed cereals, nuts, seeds, fish, meat, and milk products (Alexander et al. 2008). In the human body,  $Mg^{2+}$  mainly exists as storage form, and **only a small amount is present extracellularly in serum**. The concentration of  $Mg^{2+}$  in serum ranges from 0.5 to 1.05 mM, and its homeostasis is maintained through its absorption, reservoir, and excretion process by various organs such as the gut, bone, and kidney. Besides these organs, several hormones, namely vitamin D, parathyroid hormone, and estrogen, are involved in the regulation of normal level of  $Mg^{2+}$  (Al Alawi et al. 2018). Alteration in the level of  $Mg^{2+}$  may lead to hypomagnesemia or hypermagnesaemia. Hypermagnesaemia is characterized by neurologic and cardiac abnormalities like confusion, coma, widening of QRS complex, PR interval prolongation,

and cardiac arrest. Whereas hypomagnesemia is manifested as tetany, convulsion, and cardiac arrhythmia (Alexander et al. 2008). Clinical and preclinical studies revealed that the  $Mg^{2+}$  level is found to be low in various pathological conditions such as migraine, diabetes, osteoporosis, asthma, preeclampsia, cardiovascular diseases (CVD), and its correction is an important treatment strategy for these conditions (Gröber et al. 2015; Dolati et al. 2019; Euser and Cipolla 2009; Li et al. 2017; DiNicolantonio et al. 2018b). Various factors may associate with  $Mg^{2+}$  deficiency (Fig. 2). In pathological conditions, various  $Mg^{2+}$  salts may also be used as a source of  $Mg^{2+}$  (Table 1) (Pham et al. 2014; Gröber et al. 2015; Schwalfenberg and Genuis, 2017; Ahmed and Mohammed, 2019).



**Fig. 2** Factors associated with magnesium deficiency

**Table 1** Various clinically available magnesium supplements with their uses

Magnesium supplement	Elemental content (%)	Bioavailability (%)	Particular uses
Magnesium oxide	60	4	Effervescent magnesium oxide is better absorbed (8%) than tablets
Magnesium carbonate	45	15–40	Treatment of hypomagnesaemia, heart burn, stomach upset and acid indigestion
Magnesium sulphate	10	4	Most commonly used clinical supplement
Magnesium hydroxide	42	4	Antacid and a cathartic
Magnesium citrate	16	12	Nephrolithiasis
Magnesium lactate	12	12	Treatment of hypomagnesaemia vomiting or diarrhoea or in gastrointestinal diseases
Magnesium chloride	12	12	Treatment or prevention of hypomagnesaemia
Magnesium aspartate	10	41–45% (for 5 mg)	To treat fatigue and muscle hyper excitability

## Fate of magnesium in the body

### Absorption

Even though 300 mg of  $Mg^{2+}$  is ingested under physiological conditions, only 24–75% is absorbed

depending up on the its reserve and its level in consumed foods (Long and Romani 2014). Absorption occurs after 1 h of ingestion and becomes stable after 2–2.5 h for up to 4–8 h, and then it declines (Schuchardt and Hahn 2017). It is reported that about 65% of  $Mg^{2+}$  is absorbed upon its low intake, and only

11% is absorbed upon its high intake. Thus, the absorption rate is inversely linked with its intake (Rude 1989; Seo and Park 2008). Various exogenous and endogenous factors influence the absorption of  $Mg^{2+}$ . Advanced age and endogenous factors like inflammatory bowel diseases, short bowel syndrome, etc., abate its absorption. Exogenous factors that increase its absorption include low or indigestible carbohydrates, namely inulin, mannitol, and lactose. Simultaneously, the presence of phylate, oxalate, and non-fermentable fibers impair its absorption (Schuchardt and Hahn 2017).

$Mg^{2+}$  present in the diet is absorbed from the apical side of intestinal epithelial cells and it is then released into the blood through the basolateral side via  $Na^+/Mg^{2+}$  exchanger (Long and Romani 2014).  $Mg^{2+}$  is absorbed through enterocytes into the bloodstream via two pathways, primarily by active transcellular transport (saturable) and secondarily by passive paracellular transport (not saturable). The major uptake (80–90%) mechanism is passive paracellular transport in the small intestine. This process is facilitated by a  $Mg^{2+}$  concentration of about 1–5.0 mmol/L and a positive lumen voltage of about 15 mV (Gröber et al. 2015). The process is regulated by small transmembrane proteins referred as ‘Claudins’ (Schuchardt and Hahn 2017; Ahmed and Mohammed 2019; Gröber et al. 2015). Under reduced dietary intake of  $Mg^{2+}$ , absorption switches to active transcellular transport, which occurs at large intestine mediated by Transient Receptor Potential Channel of Melastatin 6 and 7 (TRPM 6 and 7) (Ahmed and Mohammed 2019).

#### *Storage, transport and exchange*

An average adult human body contains about 24 g or 1000 mmol of  $Mg^{2+}$ , of which 99% exist as storage form, 1% is available as in extracellular form in serum and red blood cells (RBC). Intracellular and serum magnesium concentrations range from 5 to 20 mmol/L and 0.76–1.15 mmol/L, respectively. Intracellular  $Mg^{2+}$  exists mainly as ionized form (1–5%), as bound with the proteins, and as in combination with the adenosine triphosphate (ATP) (Jahnen-Dechent and Ketteler 2012). Serum  $Mg^{2+}$  exists mainly as ionized form (55–70%), bound with the proteins (20–30%), and 5–15% of  $Mg^{2+}$  exist as sulphate, bicarbonate & phosphate salts (Swaminathan 2003). In RBCs, it is found to be relatively high with a range of around

1.65–2.65 mmol/L. In case of  $Mg^{2+}$  deficiency, a normal serum level is maintained by pulling it out from the RBCs. Thus RBC  $Mg^{2+}$  is considered as one of the good marker for  $Mg^{2+}$  deficiency (Razzaque 2018). The major storage sites for  $Mg^{2+}$  include bone (60%), muscle (20%), and soft tissues (19%) (Al Alawi et al. 2018). In bone, it exists as hydroxylapatite crystalline structure, which plays an important role in maintaining the normal serum level of  $Mg^{2+}$ , and may get affected at the time of deficiency (Gröber 2019).  $Mg^{2+}$  content in bone is declined with age, and only one-third of it is available for ionic exchange to maintain the extracellular level (Jahnen-Dechent and Ketteler 2012; Gröber et al. 2015). The list of available  $Mg^{2+}$  detection tests and significances are shown in Table 2 (Bharadwaj et al. 2014; Razzaque 2018; Al Alawi et al. 2018).

Different tissues respond in diverse ways towards the  $Mg^{2+}$  exchange. For example, in the heart, kidney, and adipocytes, the exchange of  $Mg^{2+}$  occurs within 3–4 h. Conversely, in the brain (10%) and skeletal muscle (25%), the exchange of  $Mg^{2+}$  occurs after 16 h or more. In lymphocytes, it needs more than 40 h to exchange about 5–7% of  $Mg^{2+}$  (Vormann 2016; Romani 2011a, b; Maguire and Cowan 2002). Another reason for the limited exchange of  $Mg^{2+}$  is its binding with water, restricting the bare ion entry through the membrane. This situation is common to all ions but is greater for  $Mg^{2+}$  because the radius of its hydrated moiety formed with water is 400 times larger than its ionic radius (Maguire and Cowan 2002).

#### *Excretion*

The kidney plays an important role in the maintenance of serum  $Mg^{2+}$  level. In a day, around 2400 mg of  $Mg^{2+}$  is filtered by glomeruli; from that, only 100 mg is excreted, and 95% is reabsorbed back. The absorption process occurs at the thick ascending Loop of Henle (65%) and in distal convoluted Tube (DCT) (30%) (Saris et al. 2000; Seo and Park 2008; Al Alawi et al. 2018). The process at the thick ascending loop is facilitated by various transporters like paracellin1/claudin16 and 19. Transport in DCT is mediated by TRPM6 (Gröber 2019; Ahmed and Mohammed 2019; de Baaij et al. 2015). The abnormalities in the functioning of these transporters of  $Mg^{2+}$  may lead to various diseases and are listed in Table 3 (Kolte et al. 2014; de Baaij et al. 2015; Pham

**Table 2** List of available magnesium detection tests with significances

Laboratory tests	Importance
Red blood cell magnesium concentration	Reflect the actual magnesium status
Non-invasive intracellular mineral-electrolyte analysis (EXA)	To detect tissue level of magnesium
Hair mineral analysis test	Indicates the overall body chemistry and health status
Serum magnesium level	Less likely related with body magnesium content because it represent only 0.3%
24 h excretion in urine or fractional excretion	More than 10–30 mg in 24 h excretion or above 2% in fractional excretion indicates renal wasting
Magnesium loading test	For the assessment of Intestinal and bone status of magnesium
Isotopic analysis of magnesium	<sup>26</sup> Mg was used to evaluate absorption of magnesium from the gastrointestinal tract, But its limited to research purposes
Serum magnesium/calcium quotient	Sensitive indicator of magnesium status and turn over

et al. 2014). Genetic disorders associated with the mutation of Mg<sup>2+</sup> transporters are listed in Table 4 (de Baaij et al. 2015; Seo and Park 2008).

### Cellular roles of magnesium

Extracellular and intracellular Mg<sup>2+</sup> play various physiological roles. Usually, the concentration of negative ions in cells is higher than that of the cations;

therefore, various metal ions can act as counter ions and intracellular buffers. This includes calcium, magnesium, sodium, and potassium. Positively charged Mg<sup>2+</sup> serves as a counter ion to interact with negatively charged molecules such as ribonucleic acid (RNA), deoxyribonucleic acid (DNA), reactive oxygen species (ROS), and ATP. Mg<sup>2+</sup> is thereby involved in the stabilization of DNA/RNA, modulation of enzyme activities, regulation of ion channel

**Table 3** List of magnesium transporters in different organs and diseases associated with its abnormalities

Transporter	Expression	Associated diseases
Members of the Cyclin M (CNNM)		
CNNM1	Brain	Urofacial Syndrome 1 and Jalili Syndrome
CNNM2	Kidney	Hypomagnesemia with seizure and mental retardation
CNNM3	Ubiquitous expression	Pneumonic Tularemia and Jalili Syndrome
CNNM4	Intestine	Jalili syndrome
Transient receptor potential melastatin cation channels		
TRPM6	Kidney, intestine	Hypomagnesemia with secondary hypocalcemia
TRPM7	Ubiquitous	Cardiac fibrosis, atrial fibrillation, anoxic brain injury
Solute carrier family 41 member		
SLC41A1	Ubiquitous	Preeclampsia, nephronophthisis, Parkinson disease
SLC41A2	Ubiquitous	Insulin-dependent diabetes mellitus, Epstein-Barr virus infection and Neoplasia
Mitochondrial RNA splicing 2 Mrs2	Ubiquitous	Large congenital melanocytic nevus and Osteopetrosis
Paracellin-1	Ascending limb of loop of Henle	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
Mg <sup>2+</sup> + transporter 1 MagT1	Ubiquitous	X-linked Mg <sup>2+</sup> + deficiency with Epstein-Barr virus infection and neoplasia

**Table 4** Examples of genetic disorders responsible for causing magnesium deficiency along with genes involved

Diseases	Affected genes	Features
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis type 1 (FHHNC1)	Claudin 16 (CLDN16)	Renal magnesium and calcium wasting, nephrocalcinosis and hypomagnesemia
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis type 2 (FHHNC2)	Claudin 19 (CLDN19)	Severe hypomagnesemia accompanied with nephrocalcinosis and hypercalciuria Ocular defects such as significant myopia, macular colobomata, and horizontal nystagmus
Hypomagnesemia with secondary hypocalcemia (HSH)	Transient receptor potential melastatin type 6 (TRPM6)	Low levels of calcium and magnesium in serum leading to neurological and muscular complication
Isolated autosomal recessive hypomagnesemia (IRH)	Epidermal growth factor (EGF)	Declined serum and urine magnesium level, Seizure precipitation and psychomotor retardation
Autosomal dominant hypomagnesemia (ADH)	KCNA1	Muscle cramps, weakness, tetanic episodes, and tremor. Reduced serum magnesium level
Hypomagnesemia with seizures and mental retardation (HSMR)	Cyclin M2; CNNM2	Reduced serum magnesium level without affecting other electrolytes seizures, loss of consciousness, loss of muscle tone, headaches and staring
Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance/epilepsy, ataxia, sensory neural deafness and renal tubulopathy syndrome	KCNJ10	Patients experiences electrolyte imbalance with hypokalemic metabolic alkalosis, severe hypomagnesemia, renal Na <sup>+</sup> , K <sup>+</sup> and Mg <sup>2+</sup> wasting
Isolated dominant hypomagnesemia (IDH)	FXD domain containing ion transport regulator 2 (FXD2)	Convulsions and hypomagnesemia
Renal cysts and diabetes syndrome (RCAD)	Hepatocyte nuclear factor 1B HNF1B	Hypomagnesemia, renal cyst genital and pancreatic abnormalities
Transient neonatal hyperphenylalaninemia and high urinary levels of primapterin HPABH4D	Pterin-4-alpha-carbinolamine dehydratase; PCBD1	Hypomagnesemia, renal Mg <sup>2+</sup> wasting, maturity-onset diabetes of the young(MODY5)-like diabetes
Gitelman's syndrome	SLC, solute carrier; SLC12A3	Hypomagnesemia and hypokalemia are the cardinal symptoms with tetany, paresthesias, and chondrocalcinosis
Bartter's syndrome type 1	SLC, solute carrier; SLC12A1	Salt wasting, elevated plasma renin, aldosterone levels, hypokalemic alkalosis and low BP
Bartter's syndrome type 2	KCNJ1	
Bartter's syndrome type 3	CLCNKB	
Bartter's syndrome type 4	BSND	
Kearns-Sayre syndrome	Mitochondrial deletion	Retinopathy, external ophthalmoplegia and cardiac conduction defects

functioning, and protection of the cell from oxidative stress. So a disturbance in the Mg<sup>2+</sup> level may impair these functions and contribute to pathological conditions (de Baaij et al. 2015; Wolf and Trapani 2008; Yamanaka et al. 2019).

Intracellular Mg<sup>2+</sup> is important to regulate various biochemical reactions involved in protein synthesis, energy metabolism, and signal transduction (Terasaki

and Rubin 1985; Stangherlin and O'Neill 2018). Furthermore, it participates in the intracellular signaling process by promoting protein kinase activity. Phosphorylation of protein kinase is a vital step in signal transduction, which is carried out by transferring a phosphate group from ATP to residue side chain containing serine, threonine, or tyrosine. Mg<sup>2+</sup> is involved in the transition phase of phosphate group

transfer (Knappe et al. 2015). Affinity analysis studies reported the need for a low binding free energy for ATP to bind with protein kinase in the presence of  $Mg^{2+}$ , which points out its role in enhancing the binding affinity of ATP to protein kinase (Yu et al. 2011). It protects cells from free radicals due to its free radical scavenging property. Intracellular  $Mg^{2+}$  participates in the maintenance of genome stability by acting as a cofactor for enzymes involved in the DNA repair process and by acting as a competitive inhibitor of DNA damaging agents. Extracellular  $Mg^{2+}$  participate in the ion channel regulation, especially the NMDA receptor of glutamate and is important in maintaining normal neuronal functions (Yamanaka et al. 2019). Nerve cells are communicated through electrical and chemical signals.  $Mg^{2+}$  controls the strength of channel protein at the gap junction in the electrical synapse. Besides,  $Mg^{2+}$  influx is triggered in the neuron at the time of chemical synapse mediated activities. Hence  $Mg^{2+}$  is important for regulating electrical and chemical neuronal communication; it implies its role in synaptic plasticity and neuronal network generation (Yamanaka et al. 2019).

#### Role of magnesium in brain

The cytosolic  $Mg^{2+}$  level in the brain is estimated by  $P^{31}$  Magnetic resonance spectroscopy ( $^{31}P$  MRS) and is found to be 0.182 mM; which is about half that in skeletal muscle; strengthens the report of lower ATP concentration in the brain. The decreased concentration of  $Mg^{2+}$  is associated with neurological diseases by triggering several biological and metabolic dysfunctions, which is further facilitated by diminished ATP production and altered  $Na^+/K^+$ ATPase activity (Iotti and Malucelli 2011). The blood–brain barrier (BBB) plays a major role in separating extracellular fluid (ECF) from blood circulation and facilitates the transport of materials across the brain. Various substances are transported across BBB to maintain the ionic concentration gradient between ECF and the extracellular space.  $Mg^{2+}$  concentration in ECF is higher than that in the cerebrospinal fluid (CSF) and plasma; this indicates that  $Mg^{2+}$  is actively transported to the brain. Similarly, the concentration of  $Mg^{2+}$  in CSF is higher than that in plasma, implying the active transport mechanism involved in  $Mg^{2+}$  transport. The concentration of  $Mg^{2+}$  in CSF is interrelated with various brain functions and reported

to be altered in various neurological disorders. Although the mechanism involved in the transport process of  $Mg^{2+}$  across the brain is still not clear, *in vitro* studies indicate the expression of various transporters like Transient Receptor Potential Channel of Melastatin and Magnesium transporter 1 (MagT1) in human brain endothelial cells (Yamanaka et al. 2019). Administration as organic salts and as combined form with polyethylene glycol (PEG) were tried to improve the brain delivery of  $Mg^{2+}$ , but, not found to be effective in correcting its altered level (Wang et al. 2017; Lee et al. 2010; Busingye et al. 2016).

$Mg^{2+}$  concentration in the brain is related to neuronal excitation, mediated by various neurotransmitters, including glutamate, which acts on the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA), N-methyl-D-aspartate receptor (NMDA), kainite, and metabotropic receptors present on the postsynaptic membranes. Physiologically at normal membrane potential ( $-70$  mV), the NMDA receptor is blocked by the  $Mg^{2+}$  so that glutamate can act only on the AMPA receptor. Activation of AMPA facilitates the ionic movement across the neuronal membranes, resulting in a rise in the potential to more than  $-60$  mV, which removes the  $Mg^{2+}$  block and thus activates NMDA receptors. Deficiency of extracellular  $Mg^{2+}$  results in the hyper-excitation of neurons due to NMDA over-activation. In addition to the NMDA receptor,  $Mg^{2+}$  can regulate the gamma-aminobutyric acid A receptor ( $GABA_A$ ) receptor, which is inhibitory in nature. The activation of  $GABA_A$  receptor results in the influx of chloride ions, causing neuronal hyperpolarization and inhibition.  $Mg^{2+}$  is considered as a  $GABA_A$  receptor agonist, can acts on this receptor-like benzodiazepines, and exhibits anxiolytic activity. This effect is antagonized by flumazenil; a GABA receptor antagonist, which confirms the agonistic property of  $Mg^{2+}$  on this receptor. The low central nervous system (CNS) level of  $Mg^{2+}$  may reduce  $GABA_A$  receptor activity, resulting in higher membrane potential; may remove the  $Mg^{2+}$  blockade of the NMDA channel and contribute to excitotoxicity (Poleszak 2008; de Baaij et al. 2015). Further, if extracellular  $Mg^{2+}$  is found to be less, there is increased calcium influx, which increases the release of glutamate and hence causes excitotoxicity (Blanke and VanDongen 2008). Another vital activity of  $Mg^{2+}$  in the brain is its inhibitory effect on the oxidative stress and generation

of vasoactive peptides, namely calcitonin gene-related peptide (CGRP), Substance P, etc. Deficiency of  $Mg^{2+}$  resulted in increased calcium concentration, increased production of ROS, and ROS-mediated cell death.  $Mg^{2+}$  deficiency promotes the release of inflammatory mediators like interleukin and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) via the activation of the substance P. Furthermore,  $Mg^{2+}$  is involved in the activation of nitric oxide synthase, increases the production of nitric oxide (NO); which is involved in various functions like vasodilation, channel regulation and release of neurotransmitters (de Baaij et al. 2015).

#### *Magnesium and neurological diseases*

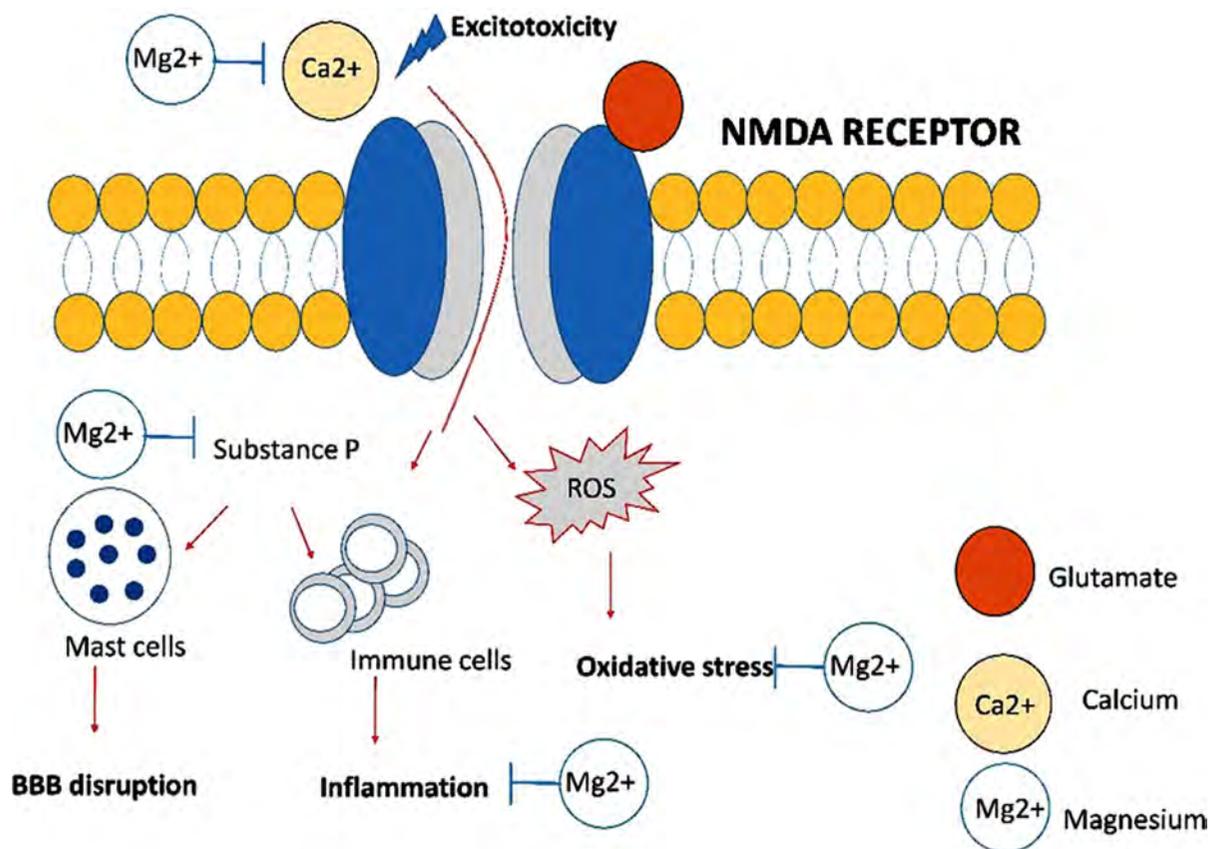
$Mg^{2+}$  deficiency has been reported in various brain-related diseases like migraine, stroke, neurodegenerative diseases, depression, epilepsy, etc. It is reported that the breakdown of BBB, edema, excitotoxicity and ROS production associated with neurological diseases can be corrected by the use of  $Mg^{2+}$  (Fig. 3).

**Migraine** Migraine is a recurrent throbbing headache and is a common neurological cause of disability in the world. Migraine condition is associated with various complications like activation of NMDA receptor (may cause cortical spreading depression), the release of calcitonin Gene-Related Peptide-CGRP (causes vasodilatation), and 5-HT (Serotonin) from platelet, resulted in platelet activation. The disorder is characterized by symptoms like emesis, nausea, occasionally with photophobia and phonobia. The level of  $Mg^{2+}$  is found to be less in serum and CSF of patients with migraine (Dolati et al. 2019).  $Mg^{2+}$  exhibited anti-migraine activity by inhibiting the activation of NMDA receptor, CGRP release, and hyper aggregation of the platelet.  $Mg^{2+}$  acts in migraine by various mechanisms like counteracting cortical spreading depression, modulating neurotransmitter action (serotonin, nitric oxide, and glutamate), increasing ATP production, decreasing platelet aggregation, and by its neuroprotective and anti-inflammatory activity (Fig. 4) (Xue et al. 2019; Sun-Edelstein and Mauskop 2009; Dolati et al. 2019). Intravenous magnesium can reduce the acute migraine attacks; meanwhile, oral administration of magnesium reduces the intensity and frequency of attack (Chiu et al. 2016). Research works reports revealed that the

magnesium sulphate supplement is found to be effective in migraine with aura, but it is not effective in common attack. Whereas magnesium citrate is found to be effective in migraine without aura (Schwalfenberg and Genuis 2017; Chiu et al. 2016; Chen et al. 2016). Magnesium pidolate is reported to cross BBB rather than depositing on the bone; it has been tried to use in migraine (Maier et al. 2020).

**CNS injury** Traumatic CNS injury may results in a decrease in intracellular  $Mg^{2+}$  level to 40–60% with a 10–15% decrease in total  $Mg^{2+}$  level; which may affect the entry of glutamate and calcium into the presynaptic neuron (Sperl et al. 2019; Cook et al. 2011). This results in neurodegeneration and cell death as secondary to brain injury (Institute of Medicine (US) Committee on Nutrition 2011). Secondary injuries include diffuse axonal injury, edema (both vasogenic and cytotoxic), extra-synaptic NMDA receptor-mediated toxicity, neurogenic inflammation, oxidative stress, mitochondrial dysfunction, and inflammation. The various studies reported that  $Mg^{2+}$  deficiency accelerates the release of substance P and pro-inflammatory mediators. There are various mechanisms that mediate the neuroprotective effect of  $Mg^{2+}$  in CNS injury. The first and most important among this is through the blockade of the NMDA receptor by  $Mg^{2+}$ , which is otherwise responsible for the excitotoxicity. The second way is by providing protection against oxidative stress by reducing the generation of free radicals and hence lipid peroxidation. The third mechanism is by preserving mitochondrial membrane integrity through the decreased production of lactic acid and there by correcting mitochondrial dysfunction (Turner and Vink 2011).

**Neurodegenerative diseases** Parkinson's disease Parkinson's disease is a neurological disorder characterized by the loss of dopaminergic neurons in basal ganglia, resulted in the resting limb tremor, slowed and involuntary body movements, dyskinesia, impaired cognitive and non-motor functions (Yamanaka et al. 2019). Excitotoxicity is considered as one of the principal cause of Parkinson's disease; that may lead to loss of dopaminergic neurons. An elevated level of inorganic phosphate along with declined cytosolic free  $Mg^{2+}$  and unchanged level of phosphocreatine is reported in Parkinson's Patients.



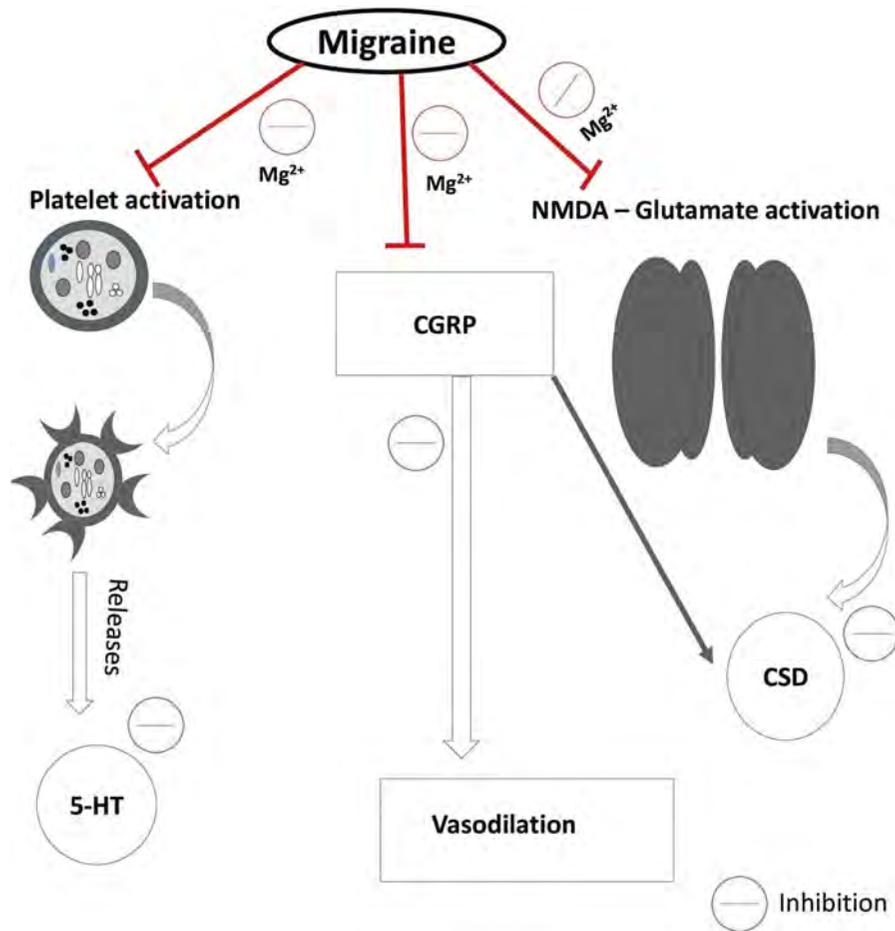
**Fig. 3** Showing the relationship between excito-toxicity and the beneficial effect of magnesium in it. Excess of calcium influx in brain may cause various complication in brain such as excitotoxicity, BBB disruption, inflammation and oxidative stress. Magnesium is found to be beneficial in neurological

diseases via correcting the above mentioned complications. i.e., inhibiting calcium influx, substance P production, inflammation and oxidative stress. *ROS* reactive oxygen species, *NMDA receptor* N methyl D aspartate receptor, *BBB* blood brain barrier

The possible mechanisms that cause Parkinson's diseases are mitochondrial damage associated with increased free radical production, unfolded protein retention, and endoplasmic stress. Mitochondrial dysfunction resulted in the aggregation of  $\alpha$ -synuclein, which is a presynaptic neuronal protein. Aggregation of  $\alpha$ -synuclein with iron initiates oxidative stress, resulting in the combination of Parkin and DJ1 genes, which prevent unfolded protein destruction. Usually, the misfolded protein aggregates and damaged organelles are degraded by autophagy, a process carried out by lysosomes. The impairment of this pathway leads to the accumulation of synuclein. Mg<sup>2+</sup> transporter, SLC41A2 is located in PARK 16 gene, which is reported to have a role in Parkinson's disease progression (de Baaij et al. 2015). Mg<sup>2+</sup> is effective in the treatment of Parkinson's

disease via two mechanisms. Primarily by inhibiting the aggregation of  $\alpha$ -synuclein with iron and other metals. The second mechanism is by having a regulatory effect on the mTOR pathway (mTOR pathway) involved in the deactivation of the autophagy process responsible for the accumulation of synuclein (Yamanaka et al. 2019). Mg<sup>2+</sup>, by regulating the mTOR pathway, reduces synuclein formation and protects the dopaminergic neurons. (Kirkland et al. 2018; Yamanaka et al. 2019). Furthermore, the prevention of neuro-inflammation by Mg<sup>2+</sup> also contributes an additional protective effect in PD treatment.

**Alzheimer's disease** Alzheimer's disease (AD) is a neurological disorder with loss of cholinergic transmitter in CNS and affects primarily the cognitive



**Fig. 4** Anti-migraine mechanism of action of magnesium: Migraine is due to mainly three reasons such as platelet activation, CGRP release and cortical spreading depression. Magnesium exhibiting its antimigraine action through inhibiting platelet aggregation, serotonin release, inhibiting CGRP

mediated vasodilation, and inhibiting CSD. 5 HT-serotonin, *CGRP* calcitonin gene related peptide, *NMDA* N methyl D aspartic acid receptor, *CSD* cortical spreading depression

function. This disease is characterized by the accumulation of extracellular senile plaques and intracellular tangles within the brain cells, along with inflammation and atrophy (Yamanaka et al. 2019). A systemic review revealed a low level of  $Mg^{2+}$  in CSF and hair of AD patients, without any significant change in serum  $Mg^{2+}$  level, when compared with normal subjects (Veronese et al. 2016). Extracellular  $Mg^{2+}$  is reported to control the BBB permeability of amyloid  $\beta$  plaque to ECF and enhances its clearance.  $Mg^{2+}$  exhibits anti-inflammatory property via reducing the expression of  $TNF-\alpha$  and production of pro-inflammatory mediators, which also contribute beneficial effect in Alzheimer's condition. Low extracellular  $Mg^{2+}$  initiate the cleavage of Amyloid precursor

protein (APP) by  $\beta$  secretase and  $\gamma$  secretase into C terminal fragment  $\beta$  (CTF  $\beta$ ) and  $A\beta$ ; which are neurotoxic. High extracellular  $Mg^{2+}$  switches the pathway to form soluble APP and CTF $\alpha$ , which is neurotrophic (Xue et al. 2019; Gröber et al. 2015; Kirkland et al. 2018). Further,  $Mg^{2+}$  inhibits glycogen synthase kinase-3  $\beta$  (GSK-3 $\beta$ ) enzyme (an enzyme involved in the cellular apoptotic process), reduces neuronal cell death, improves cognitive function and synaptic plasticity in sporadic rat's model of AD (Xu et al. 2014).

*Epilepsy* Anticonvulsant effect of  $Mg^{2+}$  is mediated by various mechanisms such as by antagonizing NMDA receptor, by increasing vasodilatory

prostaglandin's production, and by stabilizing neuronal membrane. Severe hypomagnesemia condition may precipitate generalized tonic-clonic seizures.  $Mg^{2+}$  is a potent modulator of seizure activity by inhibiting calcium influx through the NMDA receptor. Additionally, low  $Mg^{2+}$  content reduces the neuronal membrane surface charge and results in hyper-excitability (Yuen and Sander 2012).  $Mg^{2+}$  also has a role to act as a cofactor in the GABA synthesis, which also accounts for its anti-seizure activity. Higher intake of dietary  $Mg^{2+}$  is connected with a lower incidence of epilepsy and is thought to be mediated by decreased C reactive protein production (Yary and Kauhanen 2019).  $Na^+/K^+$ ATPase activity also changes with a decrease in the  $Mg^{2+}$  concentration and which increases the susceptibility to seizure (Haensch 2010). It is reported that depletion of  $Mg^{2+}$  prone to epileptic seizure by irritating the nervous system. Nuytten et al. 1991 studied two case reports; it indicates that intractable epilepsy is associated with  $Mg^{2+}$  deficiency (Nuytten et al. 1991). Supplementation of magnesium as magnesium sulphate has a beneficial effect in the pentylenetetrazol (PTZ) induced seizure model. Magnesium at an intermediate dose of 100  $\mu\text{g/mL}$

is effective in most epileptic conditions, whereas the low dose of 32  $\mu\text{g/mL}$  is effective in partial complex seizures. Thus magnesium salt exhibit a dose-dependent effect in the treatment of epilepsy (de Oliveira et al. 2011).  $Mg^{2+}$  has a beneficial role in correcting the declined levels of synaptically released GABA associated with drug-resistant epilepsy (DRE). So that  $Mg^{2+}$  supplements decrease the number of days having seizures per month, in case of DRE patients. Thus, oral magnesium supplement therapy is used as an adjuvant in DRE treatment (Abdullahi et al. 2019). In epileptic patients, the low serum  $Mg^{2+}$  may associated with fatal cardiac events and causes sudden unexpected death (Terra et al. 2011). Magnesium sulphate is also found to be effective in the treatment of porphyria-associated seizures since most of the antiepileptic drugs are contraindicated in this situation (Sadeh et al. 1991). Magnesium sulphate is also effective in the treatment of refractory status epilepticus due to febrile illness-related epilepsy (Tan et al. 2015).

## Role of magnesium in cardio vascular system

$Mg^{2+}$  plays an important role in maintaining normal physiological functions of cardiac tissue through vasodilation by reducing vascular resistance, improving blood circulation, maintaining the electrical property of the myocardium, and by its anti-inflammatory activity (Kolte et al. 2014; de Baaij et al. 2015).  $Mg^{2+}$  also exhibits effects similar to clopidogrel by inhibiting platelet aggregation and adhesion (Tangvoraphonkchai and Davenport 2018). It is reported that  $Mg^{2+}$  deficiency can induce oxidative stress, which in turn activates the inflammatory process mediated via nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B). These inflammatory events trigger the transcription of various cytokines and pro-inflammatory mediators with increased expression of matrix metalloproteinase 2 and 9. This condition ultimately results in various pathological conditions like atherosclerosis, thrombus formation, and vascular calcification (Rude 1989; Chronic et al. 1990; Tangvoraphonkchai and Davenport 2018).  $Mg^{2+}$  can also affect the ionic concentration of calcium and potassium, which has a significant role in maintaining normal cardiac physiology (Chakraborti et al. 2002).  $Mg^{2+}$  competes with calcium-binding proteins and transporters, results in a change in the concentration of intracellular unbound calcium (de Baaij et al. 2015). Extracellular  $Mg^{2+}$  acts as a calcium antagonist, inhibit calcium channel conduction, increases the excitation threshold potential, and contributes to the membrane-stabilizing effect (Kolte et al. 2014).  $Mg^{2+}$  regulates  $K^+$ , which plays a key role in myocardial conduction. Several clinical studies revealed the relationship between low intake of dietary magnesium with cardiac diseases, and it is reported that the maintenance of the normal physiological level of  $Mg^{2+}$  has a beneficial effect in various CVD (Geiger and Wanner 2012). In cardiac patients, magnesium supplementation reduces the Carotid Intima-Media Thickness (IMT), an index of atherosclerosis associated with various CVD (Kupetsky-Rincon et al. 2012; Pokan et al. 2006). The beneficial effects of  $Mg^{2+}$  on cardiac tissue are depicted in Fig. 5.

### *Magnesium and CVS disorders*

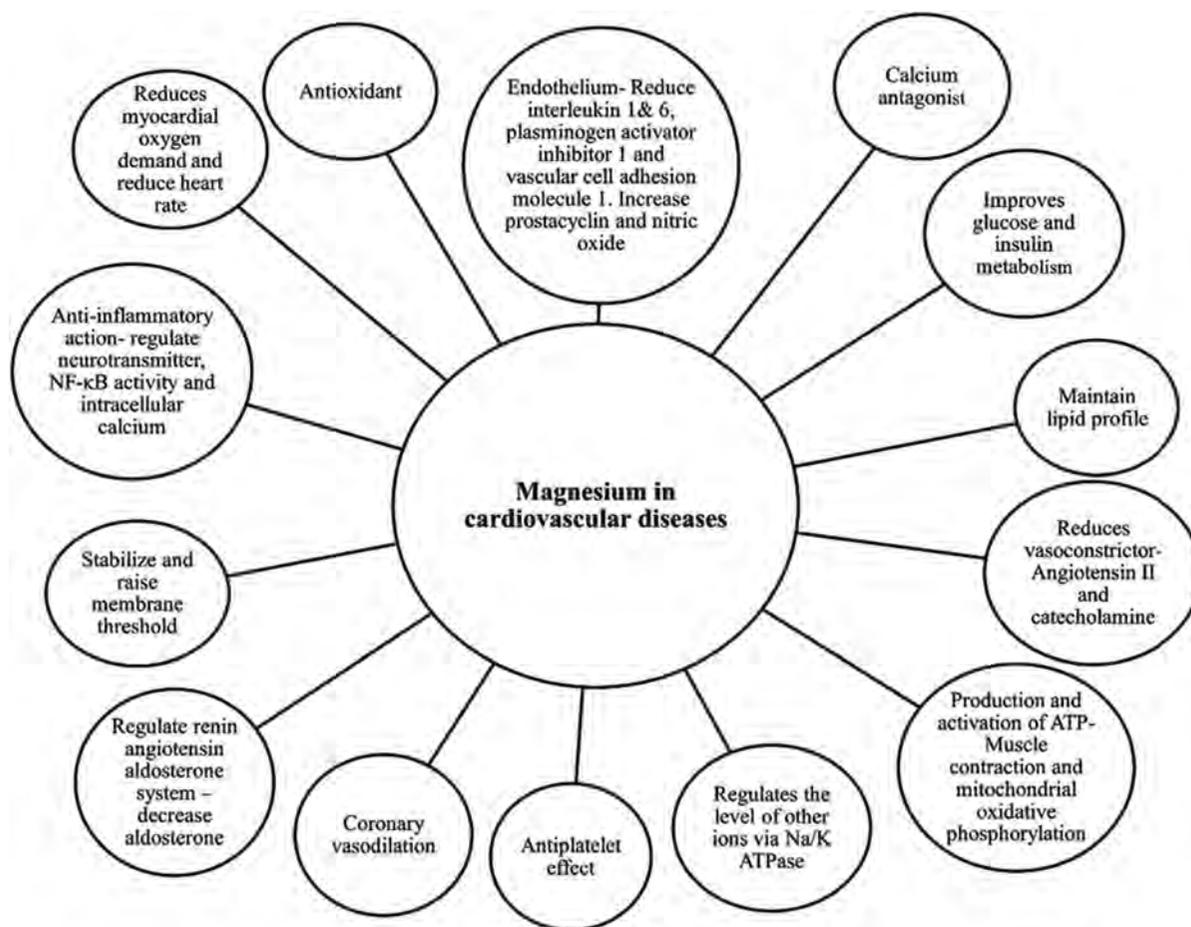
*Coronary artery diseases (CAD) and atherosclerosis* Atherosclerosis is one of the

common risk factors for triggering various CVD. Like endothelial dysfunction and hyperlipidemia, hypomagnesemia is also considered as one of the risk factors for atherosclerosis.  $Mg^{2+}$  acts as a cofactor for many enzymes like pyrophosphatase, lipoprotein lipase, etc., which are involved in lipid metabolism. The deficiency of  $Mg^{2+}$  may affect the functioning of these enzymes, resulting in altered lipid metabolism and atherosclerosis (Deepti, and Nalini 2014; Geiger and Wanner 2012). Thus  $Mg^{2+}$  is effective in improving the lipid profile and endothelial dysfunction. Also,  $Mg^{2+}$  decreases the ROS production, reduces oxidative damage, and prevents the blood clots formation by inhibiting platelet aggregation. These factors provide advantages in the treatment of CAD. As per a study conducted on CAD patients, it is reported that administration of magnesium for 6 months offered an improvement in the maximal oxygen uptake, left ventricular ejection fraction, corrected endothelial dysfunctions, and reduces platelets induced thrombosis in CAD patients (Pokan et al. 2006).

**Myocardial infarction** Myocardial infarction (MI) is resulted from the reduced blood flow to the cardiac tissue due to the formation of the plaques with interrupted myocardial oxygen supply. Commonly used treatment includes nitroglycerine and aspirin (Lu et al. 2015).  $Mg^{2+}$  provides beneficial effects through its vasodilatory effects and by preventing blood clot formation (Gröber et al. 2015; Pham et al. 2014). Anti-ischemic effect of  $Mg^{2+}$  is mediated through various mechanisms such as its calcium antagonistic property, by preserving the energy-dependent cellular process through the conservation of ATP, by decreasing the heart rate and contractility, by reducing the catecholamine-induced oxygen demand, and systemic afterload (Kolteet al. 2014). Second Leicester Intravenous Magnesium intervention trial (LIMIT 2) reported that  $Mg^{2+}$  effectively reduces mortality and left ventricular failure associated with acute mania (Gröber et al. 2015). Gyamlani et al. 2000 reported that magnesium administration after immediate post-infarction reduces the incidence of arrhythmia, pump dysfunction, and mortality associated with acute MI condition (Gyamlani et al. 2000). Studies conducted on various animal models revealed that  $Mg^{2+}$  deficiency is associated with decreased levels of endogenous antioxidants, elevated

ROS levels, and increased susceptibility of the cardiovascular system to oxidative stress (Dinicantonio et al. 2018; Kharb and Singh 2000). ROS can attack the cardiac cell membrane lipids, and cytoplasmic proteins cause nuclear and mitochondrial damage. Further, ROS can destruct the cell membrane poly-unsaturated fatty acids (PUFA), form lipid peroxides, fatty acid radicals and finally, fatty acid peroxy radicals. Thus, the free radical initiation and propagation reactions continued to form stable products like malondialdehyde (MDA); which is reported to inhibit the contractile functions of the heart and hence affect the myocardial oxygen supply. The PUFA of the subcellular organelles and sarcolemma of the cardiac myocytes are particularly susceptible to oxidative damage caused by ROS (Bandyopadhyay et al. 2005). A study conducted on 22 patients demonstrated that  $Mg^{2+}$  deficiency can exacerbate oxidative damage to post-ischemic myocardium, and the antioxidants are found to have beneficial effects in this condition (Freedman et al. 1990). A study report revealed that  $Mg^{2+}$  reduces the infarct size and mortality rate in MI patients (Antman 1996; Teo et al. 1991). A meta-analysis study indicates that  $Mg^{2+}$  has a beneficial effect in reducing arrhythmias in patients with MI (Salaminia et al. 2018). Thus magnesium supplementation is considered as an adjuvant in the treatment of MI (Rosique-Esteban et al. 2018). Some trials fail to prove its efficacy studies for introducing  $Mg^{2+}$  for MI; studies are still ongoing, owing to its low cost, ease of administration, good tolerability, and experimentally proven cardioprotective function (Kolteet al. 2014).

**Arrhythmia** Cardiac arrhythmia is a condition characterized by an irregular heartbeat rhythm that may be either too slow (< 60 beats/min) or too fast (> 100 beats/min) and may occur at any age (Du-guan 2015). Normal cardiac rhythm is maintained by various ions like sodium, potassium, and calcium (Antzelevitch and Burashnikov 2011).  $Mg^{2+}$  deficiency is one of the risk factors for ventricular and supraventricular arrhythmia (Salaminia et al. 2018). The ECG changes observed in hypomagnesemia conditions include prolonged QT interval, depressed ST segment, and low amplitude of T waves. Hypomagnesaemia arises from stress or alcoholism is also responsible for inducing arrhythmias (Ramee et al. 1985; Topol and Lerman



**Fig. 5** The beneficial role of magnesium in cardiac tissue

1983).  $Mg^{2+}$  deficiency contributes to cardiac arrhythmia by disrupting the activity of  $Na^+/K^+$  ATPase causes an imbalance between intracellular and extracellular potassium levels, impair the resting membrane and repolarization potential of normal cardiac electrophysiology (Dyckner and Wester 1981). The  $Mg^{2+}$  effectively prevents atrial fibrillation occurred after cardiac surgery, and intravenous magnesium is preferred as prophylaxis at this situation by the European association for cardiothoracic surgery and the Canadian cardiovascular society (Ho 2008; Onalan et al. 2007; Alghamdi et al. 2005; Miller et al. 2005). In addition, to this  $Mg^{2+}$  is also reported to be effective in treating Torsade's des point, digoxin induced tachyarrhythmia's, neuroleptic or tricyclic antidepressant-induced ventricular arrhythmia, and Wolff–Parkinson-White syndrome (Ho et al. 2007;

Merrill et al. 1994; Sideris et al. 1996; Zehender 1996). It stabilizes the cardiac membranes and is considered as first-line in the treatment of Torsades de pointes. Intravenous magnesium regulates the cardiac electrophysiology via normalizing atrioventricular nodal conduction, by reducing automaticity, by prolonging sinus node refractory time, via preventing the antegrade and retrograde conduction over an accessory pathway and His ventricular conduction (Rasmussen and Thomsen 1989).

**Preeclampsia** Preeclampsia is a condition associated with hypertension in pregnancy with proteinuria, contributing to an imbalance in angiogenic and anti-angiogenic growth factors (Li et al. 2017).  $Mg^{2+}$  is reported to have a beneficial effect in this situation by causing vasodilation mediated through NO production. In addition,  $Mg^{2+}$

offers beneficial effects and improve foetal outcome in preeclampsia; by down-regulating the expression of anti-angiogenic factors and by up-regulating the expression of angiogenic factors like vascular endothelial growth factor (VEGF), placental growth factor (PGF), etc. (Korish 2012; Al Alawi et al. 2018; Schwalfenberg and Genuis 2017).  $Mg^{2+}$  is also beneficial in eclampsia (seizure associated with preeclampsia) conditions by vascular and neurological mechanisms. That is, it acts as a vasodilator on peripheral and cerebral vasculature; can improve circulation and decrease peripheral vascular resistance. In addition, it protects the BBB, prevents edema formation, and has a central anti-convulsant activity (Esenet et al. 2005; Euser et al. 2008; Kaya and Ahishali 2011; Hallak et al. 1992; Sibai, 2004). A coherent, systematic review suggested that  $Mg^{2+}$  reduces the risk of maternal mortality associated with eclampsia and documented the superior effect of  $Mg^{2+}$  over standard anticonvulsants. World health organization (WHO) advised to use  $Mg^{2+}$  as a standard treatment option for eclampsia and preeclampsia (Duley and Henderson-Smart 2003a,b; Fogleman 2011; Duley et al. 2006; Ayoubi 2011). Randomized, controlled trials in eclampsia patients disclosed that only 9.4% of  $Mg^{2+}$  treated women are prone to seizure when compared with 23.1% observed in the case of phenytoin treated patients (Lucas et al. 1995). Another randomized controlled trial in preeclampsia patients revealed that 2.8% of patients treated with anti-hypertensive drugs exhibit seizure episodes and in case of magnesium received patients it is only 0.9% (Witlin and Sibai 1998).

**Hypertension** Hypertension is a major cause of morbidity and cardiovascular mortality (Kanthlal et al. 2020). Low intake of dietary magnesium and fewer amounts in the drinking water may cause  $Mg^{2+}$  deficiency, which is considered as a risk factor for developing CVD like hypertension, vasospasm, atherosclerosis, etc. Also, hypertension is frequently associated with a low serum level of  $Mg^{2+}$  (de Baaij et al. 2015; Gröber et al. 2015).  $Mg^{2+}$  deficiency results in an elevated level of vasopressin, aldosterone, and catecholamines, contributing to elevated BP (Jee et al. 2009). Besides this, hypomagnesemia results in the ineffective functioning of  $Mg^{2+}$ -driven  $Na^+/K^+$ ATP ion pumps; causing dysregulation in sodium–potassium ratio, which is elevated in

hypertensive conditions (Houston 2011; Touyz 2006). Apart from these, arterial plaque formation, inflammation, soft tissue calcification, and hardening of arteries also occurred in hypomagnesemia. The inflammation associated with  $Mg^{2+}$  deficiency triggers ROS-mediated hypertension (Long and Romani 2014). Both the extracellular and intracellular  $Mg^{2+}$  play a key role in maintaining BP via its vasodilatory property (Kolte et al. 2014; Dibaba et al. 2017). Intracellular  $Mg^{2+}$  helps to reduce the level of vasoconstrictory calcium ions; extracellular  $Mg^{2+}$  acts by downregulating endothelin 1, which facilitates vasodilation through the activation of prostacyclin  $I_2$  (Kolte et al. 2014; Tangvoraphonkchai and Davenport 2018). The BP-lowering effect of magnesium is mainly suggested to be mediated via a decrease in peripheral vascular resistance associated with its vasodilatory effect (Touyz 2006). Magnesium supplementation is reported to effectively counteract the rise in BP associated with various conditions like pre-diabetics, insulin resistance, and CVD (Dibaba et al. 2017).

**Heart failure**  $Mg^{2+}$  deficiency is commonly found in patients with congestive heart failure (CHF) (Gottlieb 1989). This may be due to several reasons like increased urinary excretion of  $Mg^{2+}$ , increased extracellular volume, and due to the effect of increased aldosterone (Dinicola et al. 2018). Use of drugs like digoxin, ACE inhibitor, and diuretics also contributed to the deficiency of  $Mg^{2+}$  in congestive heart failure. In addition, in HF patients, it is essential to maintain the balanced level of  $Mg^{2+}$  as it palliates digitalis toxicity and other hemodynamic changes (Douban et al. 1996). The altered level of  $Mg^{2+}$  may prone to lethal arrhythmia followed by sudden death in CHF patients (Bashir et al. 1993). Oral supplementation of magnesium in HF patients reduces the inflammatory mediator C reactive protein, a marker for inflammatory reactions (Almoznino-Sarafian et al. 2007). Magnesium therapy is a promising approach to correct the pro-arrhythmic potential and to stabilize the cardiac repolarisation in heart failure patients (Ince et al. 2001). In line with this result, Stephen Gottlieb et al., 1993 reported that administration of intravenous magnesium sulphate reduces the frequency of occurrence of ventricular arrhythmia in CHF patients (Gottlieb et al. 1993). Magnesium orotate effectively

improves the survival rate, clinical symptoms, and quality of life of patients with severe congestive heart failure (Stepura and Martynow 2009).

**Vascular calcification** Vascular calcification is commonly observed in patients with chronic kidney diseases, which may also be associated with cardiovascular death (Zeper and De Baaij 2019). Vascular calcification is characterized by the up-regulation of genes like Runt-related transcription factor 2 (RUNX2), bone morphogenetic protein 2 (BMP2), and elevated levels of alkaline phosphatase (ALP) activity.  $Mg^{2+}$  primarily acts by inhibiting these genes, subsequently preventing the trans-differentiation and mineralization of vascular smooth muscle cells (Bressendorff et al. 2017). Patients with hypomagnesemia are more prone to vascular calcification; as  $Mg^{2+}$  is essential to prevent the formation and development of Ca/Pi (inorganic phosphate) and apatite crystals (Ter Braake et al. 2018,2017). In CALMAG study, it is reported that administration of  $MgCO_3/Ca(OAc)_2$  and sevelamer-HCl are effective in reducing Inorganic phosphate (Pi) levels without elevating calcium levels (de Baaij et al. 2015).

#### Role of magnesium in lungs

$Mg^{2+}$  and  $Ca^{2+}$  are two important cations involved in the regulation of normal bronchial functions with competing actions.  $Mg^{2+}$ , the natural calcium antagonist, inhibits the entry of calcium in smooth muscle and is involved in releasing acetylcholine and histamine (Kercsmar 2006; Altinisik et al. 2016; Houston 2011). It also affects the bronchial vasomotor tone and lung structure (Landon and Young 1993; Mathew and Altura 1988). The therapeutic potential of  $Mg^{2+}$  in various lung disorders is mediated via reducing oxidative stress, impeding the release of substance P, inhibiting the voltage-gated calcium channel, and via its anti-inflammatory activity. Several study reports revealed that intravenous and dietary magnesium corrected the impaired pulmonary functions and improves the lung volume parameters such as vital capacity and forced expiratory volume (Britton et al. 1994). These factors help in contributing protection against various lung disorders like asthma and COPD (de Baaij et al. 2015).

#### Magnesium and respiratory disorders

**Bronchial asthma** Asthma is a respiratory disease characterized by the narrowing of the airways with inflammatory reactions.  $Mg^{2+}$  deficiency is reported in serum and intracellular components of asthma patients (Kowal et al. 2007; Shaikh et al. 2016).  $Mg^{2+}$  reduces vasoconstriction and bronchoconstriction, so that its deficiency might result in the worsening of the asthmatic condition (Kelly 2003; Song and Chang 2012; Hill and Britton 1995). In 1936, magnesium is administrated for the first time for the treatment purpose in asthma patients by Victor Haury. Nebulized magnesium is also reported to improve respiratory function (Kowal et al. 2007; Song and Chang 2012; Mohammed and Goodacre 2007; Kokotajlo et al.2014). The anti-asthmatic effect of  $Mg^{2+}$  is mediated by various actions such as calcium antagonist property, by reducing the neutrophil respiratory burst and by altering the intracellular cyclic adenosine monophosphate (cAMP) level (Cairns and Kraft 1996; Das et al. 2010; Shivanthan and Rajapakse 2014). According to the magnesium trial, in children, administration of magnesium sulphate through inhalational route (MAGNETIC) provides an improvement in asthma score. Means the Yung Asthma Severity Score (ASS) showed a modest but statistically significant improvement after 60 min of use of nebulised  $MgSO_4$  and this effect is lasted for up to 240 min (Shan et al. 2013). Reports supported that magnesium sulphate, combined with standard treatment, improves breathlessness and reduces hospitalization with superior effect in acute asthma patients.(Schwalfenberg and Genuis 2017). According to the recent Cochrane review (2017), inhaled magnesium sulphate with  $\beta_2$  agonist improves the pulmonary functions in severe acute asthmatic patients (Knightly et al. 2017; Grober et al. 2015).

**Cystic fibrosis** Cystic fibrosis is an autosomal recessive disorder due to mutation in the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene, which is involved in the regulation of liquid volume in epithelial cells. In this disease, due to the defective CFTR gene, there is the formation of thick and sticky mucus which finally obstruct the respiratory pathways (Davies et al. 2007; Rafeeq and Murad 2017).  $Mg^{2+}$  deficiency is reported in patients with cystic fibrosis and is mainly due to four reasons;

insufficient dietary intake, reduced intestinal absorption (due to pancreatic insufficiency associated with the disease), hyperglycemia associated with cystic fibrosis may trigger hypomagnesaemia and renal wasting associated with intake of drugs like  $\beta_2$  agonists, thiazides, loop diuretics, calcineurin inhibitor, amino-glycoside antibiotics etc. (Lee et al. 2015; Santi et al. 2016). Recombinant human DNase is used for treatment purposes, and magnesium is essential for its activation (Santi et al. 2016). Therefore the efficiency of the treatment is related to the  $Mg^{2+}$  status since  $Mg^{2+}$  can activate the endogenous Human DNase in sputum (Sanders et al. 2006). As per reports, oral magnesium can effectively treats cystic fibrosis in children via improving Shwachman-Kulczycki score and respiratory muscle strength. Furthermore, improvement of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) is also reported in patients receiving magnesium (Gontijo-Amaral et al. 2012). Possible benefits of  $Mg^{2+}$  in cystic fibrosis treatments are improved respiratory muscle strength, pulmonary vasodilation in the case of pulmonary hypertension, and improved mucolytic activities of both endogenous and exogenous DNase (Santi et al. 2016).

*Chronic obstructive pulmonary disease* Chronic obstructive pulmonary disease (COPD) is a persistent and progressive disorder resulting from chronic inflammation in the lungs and airways (Mathew et al., 2017). According to various observational studies, hypomagnesemia is proportionally linked with the severity of chronic lung diseases and the duration of hospital stay (Do Amaral et al. 2008).  $Mg^{2+}$  exhibits anticholinergic and antihistaminic action by inhibiting acetylcholine release from cholinergic neurons and histamine from mast cells.  $Mg^{2+}$  is also responsible for reducing neutrophilic bursting in inflammation and thereby provides anti-inflammatory action. Thus the anti-inflammatory, anti-cholinergic, and anti-histaminic actions of  $Mg^{2+}$  provide favorable effects in COPD conditions (Ni et al. 2020). In a randomized, double-blind trial, it is reported that infusion of magnesium could contribute in correction of altered parameters like functional respiratory capacity, inspiratory capacity, MIP and MEP in COPD patients (Skorodin et al. 1995). Do Amaral et al. (2012) reported that the

use of magnesium diminishes the static lung hyperinflation and improves exercise performance in COPD patients (Do Amaral et al. 2012).

#### Role of magnesium in skeletal muscles

$Mg^{2+}$  is a cofactor for number of bio-chemical reactions, such as oxygen uptake, energy production, and electrolyte balance, which have important roles in maintaining normal muscle functions (Nielsen and Lukaski 2006). Muscle contraction is highly a  $Ca^{2+}$ -dependent process;  $Ca^{2+}$  released from the sarcoplasmic reticulum binds with troponin C and myosin, resulting in the conformation change in the protein that mediates the contraction process. The  $Ca^{2+}$  antagonist nature of  $Mg^{2+}$  causes an overall relaxant effect on skeletal muscle (Jahnen-Dechent and Ketteler 2012; Schwalfenberg and Genuis 2017; Al Alawi et al. 2018; Gröber et al. 2015). Under normal conditions, the concentration of  $Mg^{2+}$  is 1000 times higher than the calcium concentration and binds with the  $Ca^{2+}$ -binding sites.  $Mg^{2+}$  is displaced by  $Ca^{2+}$ ; when it is released from the sarcoplasmic reticulum. In case of  $Mg^{2+}$  deficiency, there are more free  $Ca^{2+}$ -binding sites, and hence excess binding of calcium to these sites occurs, results in hyper-contractility (de Baaij et al. 2015). Furthermore, ATP, which requires magnesium as a cofactor, is necessary for the function of the ryanodine receptor and calcium-ATPase of the sarcoplasmic reticulum (SERCA). These two are involved in releasing and reuptake of  $Ca^{2+}$  in the contraction process (Neumann et al. 2011).  $Mg^{2+}$  is required at both the resting stage and at exercise conditions. Increased  $Mg^{2+}$  turnover during exercise creates a state of its insufficiency, which causes hypertension (Kass and Poeira 2015). Increased dietary intake of magnesium or magnesium supplements by individuals with  $Mg^{2+}$  deficiency; offers beneficial effects in their exercise performances (Nielsen and Lukaski 2006).

#### Muscle cramps

Muscle cramps are one of the prominent and recurrent features of severe or chronic hypomagnesemia. The neuronal excitation caused by  $Mg^{2+}$  deficiency may contribute to muscle cramps. The beneficial role of  $Mg^{2+}$  in muscle cramps is not clear; it is believed that the calcium antagonist property of  $Mg^{2+}$  may be

responsible for its relieving effect in muscle cramps (Pham et al. 2014; Schwalfenberg and Genuis 2017). Clinical studies have documented the beneficial effect of magnesium citrate in patients with chronic persistent leg cramps (Geiger and Wanner 2012). The efficacy of magnesium in pregnancy-associated muscle cramps is also reported; i.e., a mixture of magnesium lactate and citrate at morning (5 mmol) and evening (10 mmol) is reported to have a beneficial effect (Garrison et al. 2012). However, a Coherent systematic review and meta-analysis reported that magnesium supplementation doesn't provide any beneficial prophylactic effect in older individuals suffering from muscle cramps (Schwalfenberg and Genuis 2017).

### Role of magnesium in bones

About 50–60% of  $Mg^{2+}$  is stored in bones, out of which about 30% is at the surface as hydroxylapatite crystals along with calcium and inorganic phosphate (Pi).  $Mg^{2+}$  present at the surface of the bones is only available for ionic exchange. The remaining amount becomes an integral part of the bone and is released during the bone resorption process (Al Alawi et al., 2018).  $Mg^{2+}$  is involved in regulating the solubility of minerals, thereby maintaining the size of the crystals. Apart from this,  $Mg^{2+}$  also participates in osteoblast proliferation. Magnesium-deficient rats are reported to have declined bone mass and decreased osteoblast number.  $Mg^{2+}$  deficiency is associated with reduced vascular supply to the bones that promotes the release of tumor necrosis factor ( $TNF\alpha$ ), substance P, and interleukin  $1\beta$ , which triggers osteoclastic bone resorption. The reduced level of parathyroid hormone and 1,25-dihydroxy vitamin D3 ( $1,25(OH)_2D_3$ ) occurred in hypomagnesemia, which also worsens the bone resorption process (Castiglioni et al. 2013; Welch et al. 2017). Osteoporosis is reported to be often associated with hypomagnesemia. Osteoporosis is a multi-factorial disease that occurs due to the imbalance between the bone deposition and resorption mechanisms, associated with declined bone mass and increased fracture risks (Castiglioni et al. 2013). Immuno-histological results revealed the loss of osteoblast, diminished bone growth, augmented osteoclastic resorption, along with trabecular bone loss in magnesium-deficient rats model of osteoporosis. Since  $Mg^{2+}$  is a mitogenic agent for bone growth, its

deficiency affects the growth and formation of bone cells and bone strength (Rude et al. 2009). Decreasing Osteocalcin, a protein essential for bone formation and high parathyroid hormone and deoxypyridinoline levels, is reported in the  $Mg^{2+}$  deficient animal models. Thus these altered variables affect bone mass and strength (Weng and Webster 2013). Also, increased interleukin1 (140%),  $TNF\alpha$  (120%), and megakaryocytes (500%) count is reported in  $Mg^{2+}$  deficient animals, which indicates the increased activity of cytokines in the bone. The study indicates that  $Mg^{2+}$  has an important role in the prevention of osteoporosis (Rude et al. 2003; 1998). According to the Women's Health Initiative Study, wrist fractures are common in those females with a low magnesium level. Another study reported that magnesium, when administered at a 600 mg dose for 12 months, resulted in an 11% increase in Bone mineral density (BMD) in osteoporosis patients (Orchard et al. 2014). But the factor that limits the use of magnesium in the treatment of osteoporosis in the general population is its detrimental effect on bone (Castiglioni et al. 2013). As per study reports, it is documented that a higher intake of magnesium increases BMD, with fewer fracture risks, meanwhile reduces bone turnover in postmenopausal women and adults. Thus an increase in magnesium level beyond an optimum value is harmful to bone health. Magnesium may adversely affect the osseous metabolism and parathyroid gland functioning, leading to defects in bone mineralization. High bone  $Mg^{2+}$  inhibits the development of hydroxylapatite crystals by competing with calcium and binding to insoluble salt-forming pyrophosphate, which is not degraded by enzymes. This condition leads to osteomalacic renal osteodystrophy (Castiglioni et al. 2013).

### Role of magnesium in liver

$Mg^{2+}$  is important to carry out the normal enzymatic reactions in the liver, including fat metabolism (Liu et al. 2019). Hypomagnesemia is reported to be associated with liver diseases. There are reports demonstrated that administration of magnesium to obese magnesium deficient woman leads to a reduction in aminotransferase (ALT) and systemic high-sensitivity C-reactive protein (hs-CRP) mediated inflammation; which is not observed in individuals

with normal serum  $Mg^{2+}$  level (Rodriguez-Hernandez et al. 2010).

### *Magnesium and liver diseases*

**Liver cirrhosis** Liver cirrhosis is characterized by damage in liver structure, fibrosis with regenerative nodules and may occur as the end stage of various liver diseases (Vijayan 2014). Patients with liver cirrhosis have a lower level of intracellular and serum  $Mg^{2+}$  concentration (Liu et al. 2019). Various factors like the use of hepatotoxic drugs, exposure to toxic substances, type two diabetes, and obesity are the main reasons for non-alcoholic fatty liver diseases. At the same time, alcohol is the main factor responsible for the development of alcoholic fatty liver diseases.  $Mg^{2+}$  deficiency is associated with alcoholic and non-alcoholic fatty liver diseases (Li et al. 2018a, b). Consumption of alcohol resulted in  $Mg^{2+}$  deficiency by two mechanisms; by increasing the excretion of magnesium through lactate production and organic acid accumulation and by affecting the normal functioning of  $Mg^{2+}$  transporter in the kidney. The release of endotoxins in alcoholic fatty liver conditions activates the kupffer cell via toll-like receptor type-2 (TLRT-2). This may promote the release of pro-inflammatory cytokines and chemokines, resulting in cirrhosis (Liu et al. 2019). Alcohol-induced liver cirrhosis also contribute to the altered fatty acid and carbohydrate metabolism (Cederbaum 2012).  $Mg^{2+}$  is important for maintenance of normal mitochondrial function as its deficiency is associated with the altered fatty acid metabolism in mitochondria (Altura et al. 1996). Apart from the above,  $Mg^{2+}$  deficiency detrimentally affects the citric acid cycle pathway and fatty acid metabolism by affecting the NADH/NAD<sup>+</sup> redox potential with ROS release (Liu et al. 2019).

Albumin synthesized by the liver plays a major role in the transport of  $Mg^{2+}$  through the circulatory system. Serum albumin level is low in cirrhotic patients, so the transport of  $Mg^{2+}$  becomes limited (Liu et al. 2019). Furthermore, elevated levels of various hormones like glucagon, growth hormone, and aldosterone also favor the excretion of  $Mg^{2+}$  (Burra 2013; Ferment and Touitou 1985). Hepatic  $Mg^{2+}$  deficiency is associated with increased collagen deposition (Liu et al. 2019). PKC $\epsilon$  is the group of protein kinase enzymes that regulates the function of

various cellular proteins. Low  $Mg^{2+}$  resulted in the defective cell membrane translocation of PKC $\epsilon$ , which further limits the accumulation of  $Mg^{2+}$  in hepatocytes with increased deposition of collagen and fibrinogen, which aggravates cirrhosis (Liu et al. 2019).  $Mg^{2+}$  deficiency triggers the inflammatory processes by various mechanisms such as through the release of neuro-mediators like substance P, by up-regulating the transcription of NF- $\kappa$ B activity and by increasing the calcium content within the cells (Nielsen 2018). Thus to counteract the inflammatory processes, the liver activates various protective mechanisms which contribute to fibrosis, followed by cirrhosis (Martínez-Esparza et al. 2015).

Use of alcohol, Hepatitis B viral infection, or chronic cholestasis initiates the generation of ROS (Kundu et al. 2012). ROS are directly involved in fibrogenesis through the proliferation of Hepatic stellate cells (HSCs) (Richter and Kietzmann 2016). Consequently, various signaling pathways also get activated, including mitogen-activated protein kinase (MAPK), NF-K $\beta$  and C- myb. The expression of  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), pro-fibrotic cytokines, transforming growth factor - $\beta$ 1 and type I collagen are higher in activated HSCs (Zhang et al. 2016; Puche et al. 2013).

The beneficial effects of  $Mg^{2+}$  in the treatment of liver cirrhosis are evident from the use of magnesium as lithospermate B and acetylcysteine complex, which reduces the levels of TGF- $\beta$ 1, nitric oxide, infiltration of hepatic lymphocytes, and pseudo-lobule formation. Apart from this, magnesium lithospermate B alleviated the aspartate aminotransferase (AST) and alanine aminotransferase in serum. Further,  $Mg^{2+}$  effectively reduces H<sub>2</sub>O<sub>2</sub> induced ROS production and reduces the transcriptional activation and expression of  $\alpha$ SMA, TGF $\beta$ , type I collagen, etc. Normalizing these parameters may be responsible for its effectiveness in cirrhosis treatment (Tee et al. 2018). The third national health and nutrition examination study (NHANES III) with 13,504 patients reported that magnesium intake is beneficial in reducing mortality rate in 49% of patients with liver diseases at a border level of significance (Wu et al. 2017).

**Nonalcoholic, alcoholic fatty liver and hepatic cancer** Non-alcoholic fatty liver diseases start as simple hepatic stenosis with non-alcoholic steatohepatitis, which then progresses to liver

cirrhosis and finally results in hepatic cellular carcinomas (Eshraghian et al. 2018). One of the important mechanisms contributing to non-alcoholic fatty liver diseases (NAFLD) is insulin resistance (Park 2006).  $Mg^{2+}$  is involved in regulating the proper functioning of insulin by decreasing the tyrosine kinase activity, and its deficiency may cause insulin resistance.  $Mg^{2+}$  level is also altered in non-diabetic patients and in hepatic steatosis (Eshraghian et al. 2018).

$Mg^{2+}$  plays an important role in enzyme reaction by mediating the stability of the genome, which is important in regulating cell proliferation, differentiation, and apoptosis (Jahnen-Dechent and Ketteler 2012). Thus  $Mg^{2+}$  deficiency may impair this mechanism, causes DNA mutation or initiation of the cancer process (Błaszczuk and Duda-Chodak 2013). Liver cancer is reported to be associated with  $Mg^{2+}$  deficiency, and magnesium supplementation through drinking water is reported to have a beneficial effect in it (Wu et al. 2017). Hepatitis B virus infection (HBV) is one of the reasons for hepatocellular carcinoma. During HBV infection, the regulatory protein in Hepatitis B virus X (HBx) intensifies the Tumor growth factor  $\beta$  (TGF- $\beta$ ) activity. TGF- $\beta$  can act as a tumour promoter to induce epithelial-mesenchymal transition (EMT), which is responsible for invasiveness and metastasis associated with hepatocellular carcinoma. Magnesium provides beneficial effects by pleiotropic mechanisms like up-regulating the activity of protein phosphatase magnesium-dependent 1a (PPM1a), by blocking TGF- $\beta$  activity, and by inhibiting the transcription of tumour promoting genes (Liu et al. 2019).

#### Role of magnesium in the pancreas

$Mg^{2+}$  participates in the endocrine and exocrine functions of the pancreas. The *ex vivo* model using rabbit pancreas revealed that  $Mg^{2+}$  regulates insulin secretion. The studies using rat pancreas and insulinoma cells also supported these reports. Furthermore, clinical reports indicated increased insulin resistance in magnesium-deficient patients (de Baaij et al. 2015).  $Mg^{2+}$  acts as a cofactor for the enzymes involved in carbohydrate metabolism. In magnesium-deficient animals, insulin receptor phosphorylation and glucose accumulations are found to be impaired (Al Alawi et al. 2018).  $Mg^{2+}$  level is inversely related with the

homeostatic model assessment insulin resistance (HOMA-IR) test for  $\beta$ -cell function and insulin resistance, hemoglobin alpha 1 (HbA1), and plasma glucose levels (Long and Romani 2014). Low serum level of  $Mg^{2+}$  is reported in type 2 diabetes mellitus patients which is responsible for the decreased treatment outcome and increased mortality associated with the disease (Kostov 2019). Diabetic retinopathy, a chronic complication of diabetes, is also triggered by the inflammatory condition associated with hypomagnesemia (Kumar et al. 2019).  $Mg^{2+}$  is required to activate insulin receptors, which belong to the tyrosine class, and mediate the intracellular signaling process.  $Mg^{2+}$  deficiency disrupts the signaling process and results in insulin resistance (Barbagallo et al. 2003; Morakinyo et al. 2018).

Furthermore, hypomagnesemia facilitates the  $Ca^{2+}$  entry to adipocytes, causes oxidative stress and inflammation, which further contributes to insulin resistance (Zheltova et al. 2016). Insulin causes the  $Mg^{2+}$  to move from the extracellular to the intracellular compartment and decreases the renal tubular reabsorption process of  $Mg^{2+}$ , resulting in hypomagnesemia (Al Alawi et al. 2018). Magnesium supplementation provides beneficial effects in type 1 patients by normalizing lipid profile, HbA1c, and by reducing neuropathic incidences associated with diabetes (Shahbah et al. 2017). Clinical trials proved that magnesium is effective in gestational diabetes mellitus by reducing plasma glucose levels and by maintaining a proper lipid profile (Maktabi et al. 2018). Various mechanisms suggested to be included under these beneficial effects are by down regulating the oxidized low-density lipoprotein receptor (LDLR) and by up regulating the peroxisome proliferator-activated receptor-gamma (PPAR- $\gamma$ ) and glucose transporter 1 (GLUT-1) (Jamilian et al. 2017) expressions. However, to establish the actual efficiency of magnesium in diabetic conditions, there is a need to conduct large sample-sized clinical trials.

#### Role of magnesium in skin

Atopic dermatitis patients are presented with declined levels of erythrocyte zinc and serum magnesium levels (Makiura et al. 2004). Magnesium supplements are effective by reducing inflammation, enhancing the proliferation and differentiation of epidermal cells, by enhancing skin hydration and dermal permeability

(Proksch et al. 2005). Magnesium with ceramides has been beneficial in treating mild to moderate atopic dermatitis (Schwalfenberg and Genuis 2017). Also, magnesium can be administered through the transdermal route which can bypass the gastrointestinal tract and thereby helps to correct the serum  $Mg^{2+}$  level (Gröber et al. 2017). Magnesium is also reported to be beneficial in psoriasis therapy. Psoriasis is immune-related disease characterised by hyperproliferation with incomplete differentiation of keratinocytes (Rajitha et al. 2019).  $Mg^{2+}$  deficiency is reported in psoriatic patients, and topical magnesium therapy is one of the oldest treatment options for the disease (Shahidi-Dadras et al. 2012; Chandrasekaran et al. 2014). Topically applied  $Mg^{2+}$  can cross the stratum corneum barrier depending upon the time and concentration of exposure. Hair follicle also contributes a significant role in this permeation (Chandrasekaran et al. 2016). The advantage of this delivery mechanism is the avoidance of diarrhoea, the most common problem associated with the oral use of magnesium (Razzaque 2018). Clinical observation revealed the beneficial effect of magnesium in patients with skin allergy (Błach et al. 2007). Oral magnesium chloride effectively treats familial benign chronic pemphigus or Hailey–Hailey disease, a rare skin disease (Barde et al. 2017). Besides, magnesium supplementation is reported to be effective in the pseudoxanthoma elasticum, a genetic disorder affecting skin, eye and blood vessels (Rose et al. 2019).

#### Role of magnesium in ear

Hearing loss may be associated with multiple etiological factors like noise or drug-induced hearing loss or sudden sensory neural hearing loss. The underlying cause of hearing loss is the imbalances in various metabolic processes like ischemic, ionic, excitotoxicity, and ROS.  $Mg^{2+}$  has therapeutic potential in hearing loss because of its vasodilatory, calcium, and NMDA antagonist actions and due to its antioxidant potential (Fig. 6). The neuroprotective effect of  $Mg^{2+}$  provides additional beneficial effects in the cellular death associated with hearing loss. Moreover, it can easily cross the perilymph blood barrier and reaches the organ of Corti than any other currently existing drugs (corticosteroids) (Sendowski et al. 2011). A study conducted on the US population revealed a correlation between magnesium intake and a lower

risk of hearing loss (Choi et al. 2014). Another study conducted in 1994 reported that magnesium administration reduces noise-associated hearing damage (Attias et al. 1994).  $Mg^{2+}$ , which easily crosses the hemato-cochlear barrier, has neuroprotective and vasodilatory effects and can minimise cochlear damage (Sendowski 2006). The magnesium-treated groups have a better tolerance to all sound frequencies tested (> 10 dB hearing level) (Nageris et al. 2004).

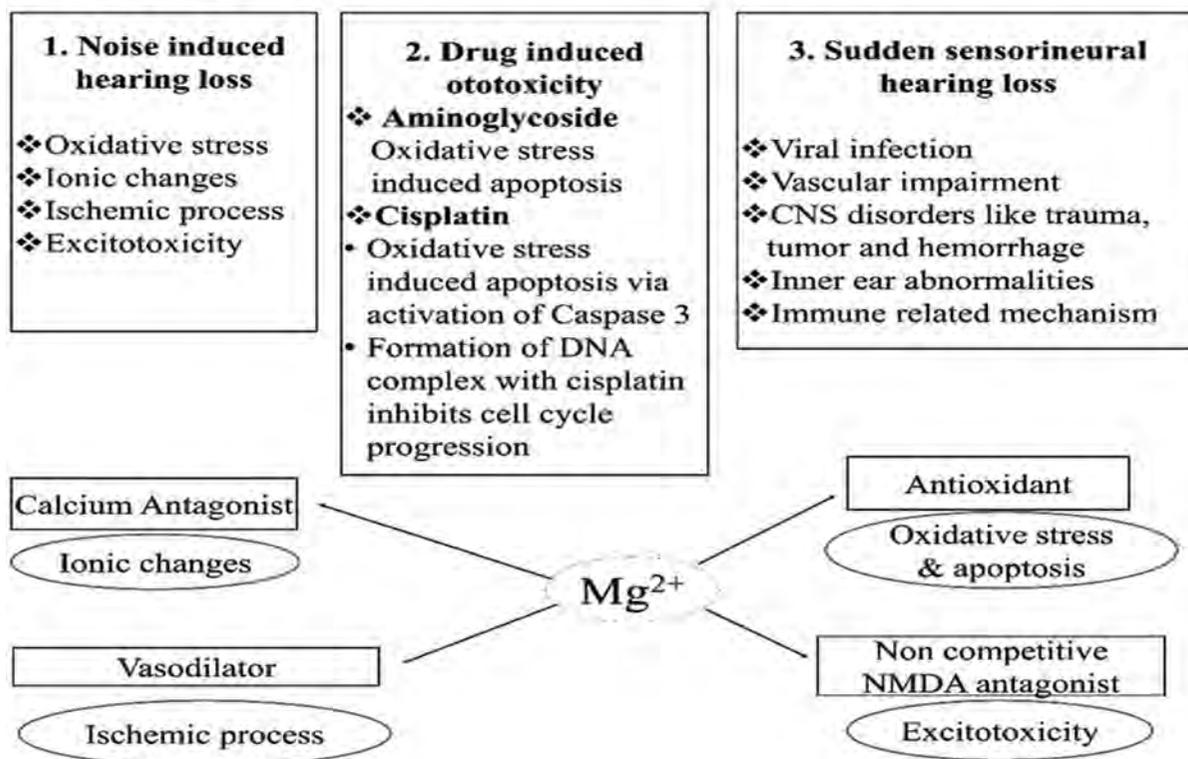
#### Role of magnesium in eye

$Mg^{2+}$  offers neurovascular protection in ocular diseases due to its vasodilatory effect achieved by reducing endothelin 1 production and by enhancing endothelial nitric oxide synthase activity (Ajith 2020). Furthermore, magnesium plays a vital role in maintaining lens homeostasis (Agarwal et al. 2013). Additionally, regulation of lens sodium pump activity, glutamate and calcium antagonist property, and the inhibitory effect on apoptosis of retinal ganglion cells; contribute to the efficacy of magnesium in ocular disease (Ajith 2020). Cataract is associated with magnesium deficiency which can be prevented and treated with magnesium supplementation (Agarwal et al. 2013; Nagai et al. 2006; 2007). Nagai et al., (2007) evaluated the effect of magnesium in cataract using the Shumiya cataract rat (SCR) model. The results showed that increased calcium content in the lens is responsible for the opacity associated with cataract, and administration of magnesium supplement is beneficial in ameliorating this effect due to its calcium antagonist property (Ekici et al. 2014). Furthermore,  $Mg^{2+}$  plays a vital role in maintaining lens homeostasis (Agarwal et al. 2013).

Glaucoma is the condition of chronic optic neuropathy that may often result in loss of vision. The rise in intraocular pressure with optic nerve damage is the main reason for glaucoma.  $Mg^{2+}$  regulates the ocular blood supply by its effect on endothelin-1 and endothelial nitric oxide expression. Additional neuro-protection is offered by its NMDA antagonistic effect (Ekici et al. 2014). The effectiveness of magnesium in correcting the blood flow and ganglion cell loss provides beneficial effects in glaucoma conditions (Iezhitsa and Agarwal 2018; Li et al. 2018a, b). Bioabsorbable coated magnesium alloy is a promising approach to develop a surgical assistive device for glaucoma (Li et al. 2018a, b). In glaucoma

## Magnesium and Ear

### Hearing Loss



**Fig. 6** Showing factors leading to hearing loss and beneficial role of magnesium in it: hearing loss is mainly due to three main reasons; noise induced, drug induced and sudden sensorineural hearing loss. The ionic change associated with hearing loss is corrected by magnesium due to its calcium antagonist action and

ischemic related problem are corrected by its vasodilatory property. Excitotoxicity in association with hearing loss is corrected by its non-competitive NMDA antagonist action. Additionally antioxidant action of magnesium is beneficial in oxidative stress and related apoptosis

patients with vasospasm, magnesium improves peripheral circulation that is beneficial in the visual field (Zulema Gaspar et al. 1995).

#### Role of magnesium in immunity

$Mg^{2+}$  is important in acquired immunity via regulating lymphocyte growth (Tam et al. 2003). An in vitro study carried out in chicken B cell line DT40 revealed that the removal of magnesium channel, TRPM7, results in cell death and can be partially corrected by magnesium supplementation (Schlingmann et al. 2007). Mutation in MagT1, a magnesium transporter, is reported in patients with X-linked immunodeficiency diseases, Epstein–Barr virus infection, and neoplasia (XMEN) (Ravell et al. 2014). Low  $CD4^+$  T

cells and defective activation of T-lymphocytes are due to the decreased magnesium influx, which fails to activate  $PLC\gamma 1$  (Li et al. 2011a, b; Li et al. 2012). The importance of magnesium for  $CD4^+$  activation is also evident from reported studies conducted in asthma patients (Liang et al. 2012). However, further studies are essential to conclude the effect of  $Mg^{2+}$  on T cell signaling.  $Mg^{2+}$  has an important role in synthesizing and releasing immune cells and other associated processes like cell adhesion and phagocytosis (Kubena 1994). Besides, it acts as a cofactor for the synthesis of immunoglobulin, CI 3 convertase, antibody-dependent cytotoxicity, macrophage responses to lymphocyte, IgM lymphocyte binding, T helper B cell adherence, substance P binding with lymphoblast, and binding of antigen to macrophage (Galland 1988; Laires and

Monteiro 2008). Indeed, the deficiency affects various immune functions like the decline in NK cell level, monocytes and T cell ratio, increased oxidative stress after strenuous exercise, and elevated cytokine IL-6 level and inflammatory events. Deficiency of  $Mg^{2+}$  may be prone to recurrent bacterial and fungal infection (Nielsen 2018).  $Mg^{2+}$  deficient animal model exhibits inflammation as the first noticeable change with elevated levels of pro-inflammatory mediators like  $TNF\alpha$  with declined anti-inflammatory cytokine levels (Galland 1988; Schmitz and Perraud 2017). The activation of immune cells like monocyte, macrophages, and polymorphonuclear cells are involved in the release of inflammatory mediators like cytokine, free radical and eicosanoids (Galland 1988). Administration of magnesium reduces leukocyte activation and oxidative damage to peripheral blood lymphocyte DNA in athletes and sedentary young men (Petrović et al. 2016). Thus,  $Mg^{2+}$  is an important factor for optimum immune cell functioning by regulating the proliferation and function of lymphocytes (Kubena 1994). In vitro studies also prove the role of magnesium in reducing leukocyte activation through its calcium antagonistic action (Laires and Monteiro 2008). Magnesium deficiency results in the stress condition that activate the sympathetic system and hypothalamic-pituitary axis causes fat accumulation and release of neuropeptides; results in the immune response followed by inflammatory cascades (Rayssiguier et al. 2010).

#### *COVID 19 and magnesium*

$Mg^{2+}$  and other elements such as zinc, selenium, and iron play an important role in the immune system. Lack of consumption of these elements may reduce the tolerance to infections and increases the disease burdens (Calder et al. 2020).  $Mg^{2+}$  can inhibit cytokine storm and hyper oxidative stress in COVID 19 patients through various mechanisms such as its antioxidant, immune-modulatory, and anti-inflammatory activities (Moh'd Nour et al. 2020). Based on the basic and clinical research study, it is evident that  $Mg^{2+}$  effectively treats respiratory diseases like asthma and pneumonia because of its anti-inflammatory, antioxidant, and smooth muscle relaxant properties (Tang et al. 2020). A substantial decrease in the need for oxygen or intensive treatment assistance is reported in elderly COVID 19 patients upon the intake

of vitamin D, magnesium, and vitamin B12 (DMB) in combination (Tan et al. 2020). Iran's clinical trial registry (IRCT) confirmed that magnesium sulphate inhalation is effective in improving respiratory symptoms such as shortness of breath, cough and oxygen saturation in COVID 19 patients (Pourdowlat et al., 2021).

#### *Newer formulation strategies for magnesium*

$Mg^{2+}$  deficiency is reported in number of neurological diseases and administration of intravenous magnesium sulphate is one of the treatment strategy for these conditions. But the CNS permeability of clinically using magnesium salts are reported to be less. To improve the CNS penetrability of  $Mg^{2+}$  few attempts are done and considered in this section. Magnesium threonate, newer organic salt of magnesium, is claimed to have greater BBB permeability than the inorganic salts. Shen et al. (2019) studied the effect of magnesium L threonate in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) induced motor deficit and dopaminergic neuron loss in mouse (Shen et al. 2019). The efficacy of magnesium threonate is proven by its beneficial effect in memory deficit and neuropathic pain; which is mediated by reducing  $TNF-\alpha$  production and by correcting the NMDA receptor dysfunction (Wang et al. 2013). Another study aims to improve the CNS availability of magnesium by combining it with PEG. This combination is found to be effective in treating unilateral cervical spinal cord injury and traumatic brain injury (Lee et al. 2010; Busingye et al. 2016). Magnesium oxide nanoparticle synthesised by the co-precipitation method exhibits good antibacterial activity against both gram-positive and negative bacteria (Imani and Safaei 2019). Another study reported that magnesium oxide nanoparticle is more effective in reducing anxiety induced by exercise than conventional magnesium oxide (Kesmati et al. 2014). The anti-cataract effect of liposomal magnesium taurate is checked in galactose-induced cataract model in rats. The formulation effectively prevents cataract genesis, which is mediated by maintaining the lens mineral homeostasis and by preventing the oxidative stress (Iezhitsu et al. 2016). A newer magnesium chloride supplement 'ChronoMag' as a dietary supplement is introduced for providing low-dose continuous magnesium with improved absorption, bioavailability, and GI tolerance

for use in health conditions associated with low magnesium levels (Dualé et al. 2018).

## Conclusion

Nutrients play major roles in regulating various vital functions of the physiological system. Magnesium is an important nutrient that plays several roles, such as to acts as a cofactor for more than 300 enzymatic reactions, promote growth via synthesis of DNA, RNA, and proteins, involved in muscle contraction, maintain normal cardiac and neurological functions. Magnesium performs various tasks as a drug through functions such as calcium antagonism, NMDA blocking, and vasodilatory action. The antioxidant and anti-inflammatory activities of magnesium provide additional protection in various disease conditions; as many diseases have oxidative stress or inflammatory reactions as background. Due to its versatility and universality in its functions, it can be considered a “master cation”. Even though it has a wide range of therapeutic activities, its functionality is not given the attention it deserves. Apart from the treatment beneficial, it also has lesser toxicity because of the body’s regulatory mechanism. The body maintains the normal level of magnesium via its absorption, storage, and excretion process. Hypomagnesemia is reported in various diseases like asthma, neurological diseases, preeclampsia, and CVD. Magnesium is obtained from various food materials and water under physiological conditions, but these sources are not satisfactory in a diseased state. There is a need for large sample size clinical trials to upgrade the use of magnesium as a standard drug. The future perspectives based on magnesium therapy strategies should include the development of the targeted delivery system to make the therapy more effective without deleteriously affecting other organ’s functions.

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## Declarations

**Conflict of interest** There is no conflict of interest in this study.

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