

**ROLE OF NUTRACEUTICALS IN THE MANAGEMENT OF DIABETES MELLITUS: A REVIEW****Rajashekar Perusomula<sup>1</sup>, Mahesh Kumar Sharma<sup>2</sup>, Priyanshu Tyagi<sup>3</sup>, Arvind Singh<sup>4</sup>, Pooja Khanpara<sup>5</sup>, Tulsil Tilva<sup>6</sup>, Vinod Gahlot<sup>7</sup> and D. Prasanth<sup>8\*</sup>**<sup>1</sup>Department of Pharmacology, Cognitive Science Research Initiative Lab, Vishnu Institute of Pharmaceutical Education & Research, Narsapur, Telangana.<sup>2</sup>Department of Pharmaceutical Science, Apex University, Jaipur, Rajasthan.<sup>3</sup>Medico-Marketing, Jagsonpal Pharmaceuticals.<sup>4</sup>Medico-Marketing, Jagsonpal Pharmaceuticals.<sup>5</sup>Department of Pharmacognosy, Smt. R. D. Gardi B.Pharmacy College, Nyara, Rajkot, Gujarat.<sup>6</sup>Department of Quality Assurance, Smt. R.D. Gardi B.Pharmacy College, Nyara, Rajkot, Gujarat.<sup>7</sup>Department of Pharmacy, HIMT College of Pharmacy, Greater Noida, Uttar Pradesh.<sup>8</sup>Dept. of Pharmacology, School of Pharmacy, University management and technology, Gopalpur, Balasore, Odisha.**\*Corresponding Author: D. Prasanth**

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**ABSTRACT**

A state of hyperglycemia caused by a deficiency of insulin production, action, or both characterizes diabetes, a complicated, chronic illness. Numerous nutraceuticals employed in clinical practice have been demonstrated to target diabetes, favorably influencing a range of biochemical & clinical outcomes. In many conventional medical systems, hypoglycemic drugs are used to treat, control, and prevent diabetes mellitus. These medicines are made from various plants. These extracts of plants have shown a clinically significant advantage in maintaining healthy blood sugar and lipid profiles. The use of natural products, herbal cures, and nutraceuticals in therapies has grown recently on a global scale. Conventional therapy options that are available as synthetic drugs do not satisfy the expectations of therapeutic demands for healing a variety of pathological diseases. Nutraceuticals offer an additional hopeful therapeutic option for diabetes with fewer adverse effects than herbal drugs. Nutraceuticals are characterized as non-specific biological therapies that use only organic products to maintain and advance health, halt the progression of cancer, and treat symptoms. Nutritional supplements are said to have potent disease-prevention, disease-cure, and health-promoting qualities. This study aims to highlight and comment on certain of the most widely used nutraceuticals for diabetes prevention.

**KEY-WORDS:** Nutraceuticals, Diabetes Mellitus, Insulin, Phytoconstituents, Micro-nutrients.**INTRODUCTION**

Unbalanced human behavior brought on by the industrial age, mechanistic lifestyle, fast-paced living, extended workdays, and many mental challenges, as well as a disconnection from natural resources, has increased the incidence of metabolic disorders (such as diabetes and obesity), cancers, cardiovascular conditions, and mental illnesses.<sup>[1]</sup> One of the significant health problems, diabetes mellitus (DM), has gained international attention. Diabetes Mellitus is a complicated metabolic condition characterized by the emergence of insulin resistance, poor insulin signaling, aberrant sugar and lipid metabolic processes, subclinical inflammatory processes, and elevated oxidative load levels. According to the 10th edition of the International Diabetes Federation (IDF) Atlas, 537 million individuals worldwide—or 1 in 10 adults aged 20 to 79—have

diabetes.<sup>[2]</sup> It was predicted that by 2040, there will be 640 million diabetes individuals worldwide.<sup>[3]</sup> The repercussions of this metabolic condition, such as a rise in blood sugar, blood lipid levels, and blood pressure, have been reported.<sup>[4]</sup> Compared to its macro-vascular problems, such as peripheral artery disease, coronary artery disease, and cerebrovascular accident, micro-vascular complications, such as diabetes, nephropathy, and retinopathy, are claimed to be more common.<sup>[5]</sup>

People are becoming more interested in dietary supplements, nutritional treatment, phytotherapy, and nutraceuticals as a result of their frustration with harmful synthetic pharmaceutical medicines and profound worry about how to preserve their wellness with healthier and efficient natural goods.<sup>[6]</sup> A meal with medical-health benefits, such as the treatment and prevention of disease,

is referred to as a nutraceutical. Natural functional/medical foods or bio-active phytochemicals that promote health, fight illness, or work as medicines are also referred to as nutraceuticals.<sup>[7]</sup> Depending on their focus, these nutraceuticals often contain the appropriate quantity of vitamins, lipids, proteins, carbs, minerals, or other essential components.<sup>[8]</sup> Worldwide, traditional medicinal herbs are utilized to treat a variety of diabetes manifestations. Due to their efficiency, lack of negative side effects, and affordable price, herbal medications are frequently given.<sup>[9]</sup> Investigation into these substances derived from conventional medicinal plants has therefore become more crucial.<sup>[10]</sup>

### Nutraceuticals

- ❖ The term "nutraceutical" was coined in 1989 by Stephen De Felice, founder and chairman of the Foundation for Innovation in Medicine in Cranford, New Jersey, by fusing the phrases "nutrition" and "pharmaceutical."
- ❖ According to De Felice's definition, a nutraceutical is a food or food component that has medicinal or health benefits, such as the ability to prevent or treat disease.<sup>[11]</sup>
- ❖ It was reportedly said by the Greek physician and inventor HIPPOCRATES, "Let food be your medicine." The guiding philosophy is to "focus on prevention".
- ❖ The following justifies the definition of nutraceuticals as a medication in European medical law
  1. It can be applied to the treatment, cure, or mitigation of a medical issue.
  2. It can be given to people in order to restore, repair, or change their physiological functioning.<sup>[12]</sup>

Nutraceuticals can include isolated nutrients, herbal items, dietary supplements, and diets, as well as processed goods including cereals, soups, oats, and drinks as well as designer meals made through genetic engineering.<sup>[13]</sup> Nutraceuticals used as anti-arthritis, for colds and coughs, sleeping issues, digestion, and prevention of some cancers, osteoporosis, hypertension control, cholesterol control, pain relievers, depressive symptoms, diabetes, heart ailments, and other chronic and progressive illnesses like Parkinson's and Alzheimer's diseases.<sup>[14]</sup>

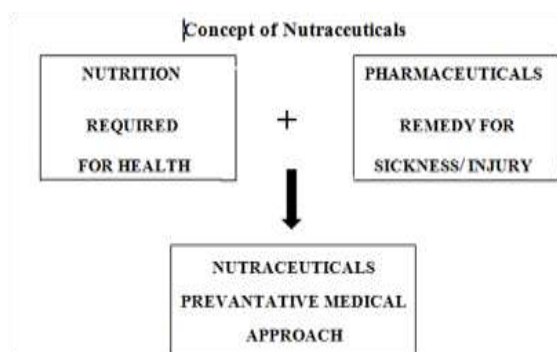


Figure 1: Concept of Nutraceuticals.

### Health benefits of Nutraceuticals

1. They have less/No side effect.
2. They may increase the health beneficial effect.
3. They may have naturally dietary supplement, without any unpleasant side effect.
4. They may increase the health value, our diet and improve medical condition of human.
5. They are easily available and economically affordable.

### Classification of Nutraceuticals

1. Functional foods- It provides nutrition's, it also contains antioxidants compounds that prevent diabetes.<sup>[15]</sup>
2. Carotenoids- They are pigmented compounds like alpha-carotene, beta carotene and beta cryptoxanthin. These compounds have antioxidant and anti-inflammatory properties, used to improve vision, prevent certain cancer and improve the immune system.<sup>[16]</sup>
3. Collagen hydrolysate – It is essential human protein secreted from skin. It has several medicinal properties.<sup>[17]</sup>
4. Dietary fibers- They're non-starchy, inadequately digested plant carbohydrates that can be found in fruits, vegetables, wheat bran, and oats.<sup>[18]</sup> It enhances digestion and lessens ulcerative colitis and Crohn's disease.<sup>[19]</sup>
5. Fatty acids- These covers all vegetable oil like olive oil.<sup>[20]</sup>
6. Phytochemicals - They're effective substances that affect the body's internal equilibrium and nerve activity, which lowers the risk of cancer. Lutein and lycopene are two of the most significant ones.<sup>[21]</sup>
7. Herbs –They are plants with no adverse effects and antioxidant capabilities, such as garlic extract and ginger, which are used to lower cholesterol and promote wound and ulcer healing.<sup>[22]</sup>
8. Probiotics- Microbes are thought to have several applications in medicine and human health. They are present in dairy products and possess antioxidant qualities. They function to control the development of the gut microbiota.<sup>[23]</sup>
9. Dietary supplements –Dietary supplements taken as tablets come in a variety of forms.<sup>[24]</sup>

### Anti-diabetic claims of Herbs

Diabetes mellitus, which affects the metabolism of lipids and carbohydrates and has a negative impact on both a person's physical and mental health, is a global threat and a metabolic illness that is rising exponentially in India.<sup>[25,28]</sup> As our understanding of the variety of this order grows, so does our need for more effective treatment. Traditional herbal remedies are employed as a secure substitute for traditional hypoglycemic medications since synthetic treatments, like as insulin in IDDM or NIDDM, have a restricted role to play and carry a high danger of developing drug resistance, which would need increasing dosage or switching medications. Due to their abundance in vital plant-based nutrients,

Ayurvedic herbs may act as "potentiators" for these medications and boost efforts to preserve the quality of life for diabetics.

### 1. Aloe vera

Aloe vera is a plant from the Asphodelaceae / Xanthorrhoeaceae family.<sup>[29]</sup> Polysaccharides, anthraquinones, and lectins having anti-diabetic properties can be found in aloe vera extract.<sup>[30]</sup> By activating  $\beta$ -cells, the gel made from the leaf pulp meat that is ingested may have hypoglycemic effects.<sup>[31,32]</sup> Numerous advantageous effects of aloe vera, including antioxidants, hypoglycemia, anti-hyperlipidemic, anti-inflammatory, and immune system regulators, have been demonstrated.<sup>[33]</sup> Positive modulation of insulin signaling pathways, restriction of glucose absorption ( $\alpha$ -glucosidase), postponed stomach emptying, and eventually improved glycemic control are some of the potential processes involved in lowering blood sugar.<sup>[34]</sup>

### 2. Garlic (*Allium sativum*)

The Liliaceae family of plants, which includes the Amaryllidaceae, includes the fragrant onion product known as garlic. Its sulfur components are what give it its nutritional and therapeutic properties.<sup>[35]</sup> Anti-hyperglycemic, antioxidant, hyperlipidemic, anti-inflammatory, anti-obesity, anti-atherosclerotic, and anticoagulant are just a few of the medicinal effects of garlic.<sup>[29]</sup> Garlic has an anti-diabetic impact through increasing insulin sensitivity and secretion. Additionally, it improves glucose uptake by over-regulating the glycolysis and gluconeogenesis-related enzymes.<sup>[36]</sup>

### 3. Turmeric (*Curcuma longa*)

Turmeric, also known as curcuma longa, provides health benefits including anti-stress, anti-depressant, antibacterial, and skin protection.<sup>[37]</sup> The most important medicinal benefits of turmeric come from its curcuminoids, which include curcumin, desmethoxycurcumin, demethoxycurcumin, and bisdemethoxycurcumin. These compounds also have anti-inflammatory, antioxidant, anti-apoptotic, anti-obesity, anti-atherosclerotic, and anti-cancer properties.<sup>[29]</sup> Diabetes wounds, arthritis, joint discomfort, anorexia, cough, gastrointestinal issues, and heart disease are all treated with turmeric.<sup>[38]</sup> Turmeric's anti-diabetic properties influence insulin secretion and insulinotropic activity, and they also control several insulin signaling pathways (AMPK, Akt), which in turn stimulates the release of insulin.<sup>[39]</sup> Turmeric reduces insulin resistance and prevents glucose,  $\alpha$ -glucosidase, and  $\alpha$ -amylase from being reabsorbed.<sup>[40]</sup>

### 4. Ginger (*Zingiber officinale*)

A blooming plant belonging to the Zingiberaceae family is called *Zingiber officinale*.<sup>[41]</sup> The three primary substances of this plant—Zingerone, Shogaol, and Gingerol—respond to distinct biological processes.<sup>[42,43]</sup> Some chemicals found in ginger have been shown to

have strong anti-inflammatory, antioxidant, and free radical scavenging activities.<sup>[38]</sup> It can control insulin signaling pathways (AMPK, Akt) associated with insulin sensitivity and boost glucose uptake in Gluc4 transport, glucose transport, and protection of beta cells,<sup>[43]</sup> insulin release/insulinotropic activity, inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase synthesis, and inhibition of enzymes related to gluconeogenesis and glycogenolysis.<sup>[44]</sup> It guards against diabetic side effects such as retinopathy, neuropathy, kidney damage, and liver damage.<sup>[29]</sup>

### 5. Cinnamon

A bushy perpetually green tree of the Lauraceae family, cinnamon is used as an anti-inflammatory, anti-fungal, and antioxidant. Diabetes, cardiovascular disease, high cholesterol levels, and hypertension can all be successfully treated with cinnamon.<sup>[38]</sup> The activation and regulation of enzymes involved in carbohydrate metabolism, such as glycolysis and gluconeogenesis, stimulation of cellular glucose uptake as well as glycogen content, and higher levels of GLUT-4 and peroxisome proliferator-activated receptors (PPARs) are just a few of the possible mechanisms by which this substance's hypoglycemic activity works.<sup>[45]</sup>

### 6. Saffron

The dried stigma of *Crocus sativus* L. is utilized as saffron, which is mostly used as a culinary flavour and colour. Crocin, picrocrocin, and safranal are the three primary secondary metabolites.<sup>[46]</sup> Saffron may help with better diabetes management and oxidative stress reduction.<sup>[47]</sup> Saffron's effects are known to be mediated by a number of different mechanisms, including stimulation of glucose uptake, inhibition of intestinal glucose absorption, inhibition of insulinase function in the kidneys and liver, inhibition of glucose production, inhibition of renal glucose uptake, correction of insulin resistance, and stimulation of  $\beta$ -cells.<sup>[48]</sup> The findings suggest that saffron may represent a fresh treatment strategy for diabetes.<sup>[47]</sup>

### 7. Fenugreek

One of the Fabaceae family of plants' annual herbaceous legumes is fenugreek. It has a variety of therapeutic effects that include antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, and anti-hyperlipidemic.<sup>[29]</sup> Fenugreek may improve insulin resistance in fat & liver cells, increase glucose absorption, increase the activity of liver enzymes including glucokinase and hexokinase, increase blood insulin levels, and increase insulin sensitivity in addition to other potential mechanisms.<sup>[49]</sup> Active substances including galactomannan, saponin, and 4-hydroxyleucine are the primary determinants of fenugreek's hypoglycemic action.<sup>[50]</sup>

Table: 1 Different plant with anti-diabetic activity.<sup>[51]</sup>

Plant	Family	Plant part
<i>Artocarpus integrifolia</i> Linn	Moraceae	Root barks
<i>Abelmoschus esculentus</i> Linn	Malvaceae	Fruits
<i>Acacia arabica</i>	Leguminosae	Seeds
<i>Acacia modesta</i> Wall	Fabaceae	Leaves
<i>Adhatoda zeylanica</i> Nees	Acanthaceae	Leaves and fruits
<i>Camellia sinensis</i>	Theaceae	Leaves
<i>Casearia esculenta</i>	Flacourtiaceae	Roots
<i>Cassia auriculata</i> Linn	Leguminosae	Flowers
<i>Catharanthus roseus</i>	Apocyanaceae	Aerial parts
<i>Chamaemelum nobile</i>	Asteraceae	Leaves
<i>Aegle marmelos</i>	Rutaceae	Root bark, fruits and leaves
<i>Allium cepa</i>	Liliaceae	Bulbs
<i>Aloe vera</i> Linn	Liliaceae	Leaves
<i>Alpinia calcarata</i> Rosc	Zingiberaceae	Rhizomes
<i>Alpinia galanga</i> Willd	Zingiberaceae	Rhizomes
<i>Alternanthera sessilis</i> Linn	Amarantaceae	Whole plant
<i>Amaranthus esculents</i>	Amaranthaceae	Whole plant, oil
<i>Ampelodesma mauritanica</i> Durand	Poaceae	Roots
<i>Andrographis paniculata</i> Nees	Acanthaceae	Roots
<i>Annona squamosa</i>	Annonaceae	Leaves
<i>Artemisia pallens</i>	Compositae	Aerial parts
<i>Biophytum sensitivum</i> Linn	Oxalidaceae	Leaves
<i>Boerhaavia diffusa</i> Linn	Nyctagenaceae	Aerial parts
<i>Bridelia Retusa</i> Spreng	Euphorbiaceae	Stem barks
<i>Caesalpinia bonducella</i> Roxb	Caesalpinaceae	Seeds
<i>Tinospora cordifolia</i>	Menispermaceae	Roots
<i>Trigonella foenum -graecum</i>	Leguminosae	Seeds
<i>Triumfetta rhomboidea</i>	Liliaceae	Whole plant
<i>Viscum album</i>	Llorenthaceae	Whole plant
<i>Withania somnifera</i>	Solanaceae	Roots
<i>Psidium guajava</i>	Myrtaceae	Whole plant
<i>Pterocarpus marsupium</i> Roxb	Fabaceae	Wood and barks
<i>Punica granatum</i>	Puniaceae	Whole plants
<i>Rubus ellipticus</i> Smith	Rosaceae	Fruits
<i>Salacia reticulata</i>	Celastaceae	Leaves

### Anti-diabetic claims of different micro-nutrients

Vitamins, minerals, and other nutrients classified as micro-nutrients are those that our systems need in very little amounts to perform certain functions. They may aid in maintaining a balanced metabolism and the process by which your body turns the sugars and other carbs in your diet into energy. Alpha Lipoic Acid (ALA), Coenzyme Q10, Carnitine, Inositol, Vitamins (B12, C, D, E, H), Vanadium, and others are several of the most well-documented dietary supplements that have been shown to have an impact on diabetes.<sup>[52]</sup>

**1. Alpha-Lipoic Acid (ALA):** It is a seldom synthesized disulfide molecule that functions as a coenzyme in the mitochondrial enzyme complexes alphaketoglutarate dehydrogenase and pyruvate

dehydrogenase. A powerful antioxidant, ALA has been found to enhance insulin-mediated glucose clearance when administered intravenously. It had been applied to treat diabetes-related neuropathy.<sup>[53]</sup> A further claim made is that ALA guards against diabetic cardiomyopathy.<sup>[54]</sup> ALA, together with 13 omega 3 fatty acids, and vitamin E, improve lipid metabolism and insulin sensitivity.<sup>[55]</sup> On BMI, HbA1C, and cholesterol levels, parenterally given ALA in 15 dosages of 600 mg for 7 days showed a positive effect. This has a definite good effect on diabetic metabolic issues and erectile dysfunction.<sup>[56]</sup> It has been discovered that ALA is useful in treating diabetic distal sensory-motor neuropathy.<sup>[57]</sup>

**2. Calcium:** Calcium and vitamin D supplementation may help to preserve insulin sensitivity and thus help



prevent diabetes by suppressing secretion of parathyroid hormone (PTH) because PTH can compromise the insulin sensitivity of adipocytes (and possibly other tissues) by increasing intracellular free calcium.<sup>[58,59]</sup>

**1. Magnesium:** These functions all depend on magnesium-containing enzymes, including nerve transmission, DNA & RNA production, glucose management, and synthesis of RNA and DNA.<sup>[60]</sup> Lack of magnesium has been associated with a decrease in insulin-mediated glucose absorption. It has been shown that diabetics excrete more magnesium and have lower blood magnesium levels.<sup>[61]</sup> the value of using magnesium supplements to avoid insulin resistance.<sup>[62]</sup>

**2. Vanadium:** Vanadium may be helpful for both type 1 & type 2 diabetes mellitus because, according to research, it transports glucose to the cells in a way that is similar to that of insulin. Supplementing with vanadium also resulted in lower levels of haemoglobin A1c, cholesterol, and fasting blood sugar 50.<sup>[63-65]</sup> To increase fasting blood sugar levels, dosages of 45 to 150 mg per day may be advantageous. These dosage levels are secure and often well tolerated by patients, according to toxicological testing. When taking greater dosages (up to 400 mg/day) or during the first week of therapy, some people experience some stomach discomfort.<sup>[66]</sup>

**3. Chromium:** The micro component chromium may not be present in sufficient amounts in diabetics.<sup>[67]</sup> Supplemental chromium may raise insulin sensitivity and improve glucose tolerance in people with type 2 diabetes. Based to a meta-analysis of randomised controlled studies examining the impact of chromium supplementation on glucose as well as insulin responsiveness in healthy individuals and those with diabetes, the latter experienced a moderate but substantial improvement in glycaemic control but not the former.<sup>[68]</sup> The official stance of the American Diabetes Association is that there is conflicting data on the benefits of supplementing with chromium for diabetes.<sup>[69]</sup>

**6. Zinc:** More than 100 enzymes that regulate digestion, metabolism, and healing wounds all need on zinc to operate normally. In order to preserve the structural integrity of insulin in its hexameric form and to ameliorate defective metabolism, zinc is crucial for the synthesis, storage, and secretion of insulin.<sup>[70]</sup>

**7. Vitamin B:** The B vitamins thiamine (B1), pyridoxine (B6), biotin, folic acid (B9), and cobalamin (B12) are frequently used in the treatment of type 2 diabetes. Thiamine is frequently used to treat diabetic neuropathy since a large number of persons with neuropathy also have thiamine deficiencies. Since thiamine is poorly absorbed, substantial amounts are necessary. It has been shown that those with type 2 diabetes have reduced thiamine levels. Thiamine has been demonstrated to lower glucose and lipid levels in diabetics, despite its typical usage as a neuropathy treatment.<sup>[71]</sup>

**8. Vitamin C:** It is a chain-breaking antioxidant that, in the form of ascorbic acid, directly neutralizes reactive oxygen species (ROS) and stops the development of chain reactions that would otherwise reduce protein glycation.<sup>[72]</sup> Vitamin C also lowers the buildup of

sorbitol and lipid peroxides associated with diabetes in animal erythrocytes. Patients with type 2 diabetes who have low vitamin C levels are given 800 mg of vitamin C daily, but neither endothelial dysfunction nor insulin resistance are treated.<sup>[73]</sup>

**9. Vitamin D:** According to Liese et al., there is a seasonal variation in the disease's control and a connection between latitude and the incidence of both type 1 as well as type 2 diabetes. This reveals a detrimental relationship between sunlight and the likelihood of developing diabetes. Since pancreatic beta cells have vitamin D receptors, vitamin D is thought to reduce insulin resistance and boost insulin production. Type 2 diabetes and vitamin D insufficiency have been linked, possibly as a result of vitamin D being stored in fat, where it is fewer accessible. According to clinical studies employing calcium and vitamin D supplements, lower insulin sensitivity is caused by vitamin D deficiency, and vitamin D may lower the prevalence of type 2 diabetes.<sup>[74]</sup>

**10. Vitamin E:** It is an essential fat-soluble vitamin that works largely as an antioxidant. Diabetes has been linked to low vitamin E levels, and some evidence indicates that people who have diabetes also have lower antioxidant levels. Another study found that diabetics may require more antioxidants due to the rise in free radical generation brought on by hyperglycemia. Up to 400 IU of vitamin E daily is commonly regarded as safe. Over-800 IU levels may affect blood coagulation, even though prothrombin time monitoring in supplement studies has not shown any alterations in subject prothrombin times.<sup>[75]</sup>

## CONCLUSION

Diabetes is one of numerous illnesses or diseases affecting the metabolism of carbohydrates, fats, and proteins that affects a major portion of the global population. It is linked to reduced insulin production or resistance to insulin's effects. Patients with diabetes, both insulin-dependent and non-insulin-dependent diabetes, have long been treated using plants. Food supplements known as nutraceuticals are nutritious. Every nutrient included in this study has demonstrated notable clinical and pharmacological action. Herbal medications provide a greater degree of potency and fewer negative effects than synthetic anti-diabetic medications. Patients are increasingly requesting to utilize natural medications with anti-diabetic properties. Hypoglycaemic herbs work by boosting insulin secretion, improving the uptake of glucose by adipose and muscular tissues, decreasing glucose absorption from the stomach, and reducing hepatocyte glucose synthesis. Nutraceuticals are finding a role in clinical practice, but additional study is necessary to address critical clinical and pharmacological problems.

## Conflict of Interest

The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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