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Comparative Efficacy of Tocotrienol and Tocopherol for their Anti Diabetic Effects

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ABSTRACT

Background: Diabetes is a chronic metabolic disorder and a Global health problem. Lifestyle modifications along with addition of miro nutrients and vitamin supplementation can be helpful to delay the occurrence of its life-threatening complications. Therefore, this systematic review was carried out to identify the comparative role of tocotrienol and tocopherol isoforms of antioxidant vitamin E for diabetic patient management.

Research Question: Is tocotreinol has better anti diabetic effects as compared to tocopherol?

Methodology: This systematic review was carried out following the PRISMA protocol and guidelines. Initially 86(n) articles were included which were than sort out to finally include 05(n). This was done following the pre defined inclusion and exclusion criteria of systematic review.

Results: The results strongly supported the inclusion of tocotrienol as part of therapeutic management of diabetes mellitus. The dose can range from 200mg to 430 mg. However, no data was available to identify comparative efficacy of tocopherol.

Conclusion: Tocotreinol because of its antioxidant, anti-inflammatory and anti fibrolytic properties helps marinating the glycemic levels in diabetic patients. Besides this the emergence of diabetic complications was delayed. A clinical improvement in patients with diabetic nephropathy and neuropathy was seen as well. It was also observed that grape seed oil supplement of tocotrienol was proven beneficial as compared to sunflower oil supplement especially by lowering inflammatory markers.

Introduction

The antioxidant and lipid soluble vitamin E have eight compounds i.e α-, β-, γ-, δ-tocopherols and α-, β-, γ-, δ-tocotrienols. The main source for the synthesis of these compounds is by photosynthetic organisms like cyanobacteria, plants, algae, fungi, sponges, corals, and tunicate. However, the foremost natural source of both these compounds the oily fraction of nuts, oil seeds, almond oil, olive oil, rapeseed oil, sunflower oil, linseed oil, corn oil, and soybean oil. The source of tocotrienols, can be rice bran and palm oil, barley, oats, wheat germ, maize, hazelnuts, and in annatto oil. The highlighted sources for α-tocopherol and γ-tocopherol are sesame, soybeans, and corn oil. Despite having similar structure and antioxidant properties, these isoforms differ in their bioavailability and metabolism [1]. The other difference is the amount of saturation for hydrophobic tridecyl chain. Tocopherols have saturated phytyl

tails whereas tocotrienols have unsaturated isoprenoid side chain with three double bonds [2].

With the advent of age, many pathologies used to come on rise. The highlighted ones are the presence of hypertension, type II diabetes, cardiovascular disorders, neurological deficit etc. These all have strong relation with oxidative stress and inflammation. Here comes the significance for using anti oxidative and anti-inflammatory to slow down the disease progression in view to improve quality of life. The isoforms of vitamin E i.e tocotrienol is notorious for both the above-mentioned properties. The reported literature supports that tocotrienols inhibit pathways that are involved in nuclear factor κB (NF-κB), signal transducers, activators 3 (STAT3) and cyclo-oxygenase 2 (COX-2). These all are the ones which activate pathological inflammatory responses. Besides this they are considered as the bioactive form of Vitamin E compared to tocopherols. Hence comes the reason for its application in the therapeutics [3].

Metabolic syndrome (MetS) also known as Syndrome X and Insulin Resistance Syndrome. Metabolic syndrome (MetS) refers to the presence of three or more amongst the five co-morbidities: obesity, systemic hypertension, prediabetes/diabetes, insulin resistance, dyslipidemia with reduced HDL levels & hypertriglyceridemia leading to increased risk of cardiovascular disease. MetS involves chronic low-grade inflammation, with elevated serum interleukin 6 (IL-6), IL-1b & CRP levels [4].

It is well known that diabetes mellitus is caused by a deficiency in insulin secretion or by a low response of organs to the action of insulin. Oxidative stress also leads to development & progression of diabetes mellitus, since an exacerbated surge in production of free radicals occurs simultaneously with repressed mechanisms of antioxidant defenses resulting in cellular damage & increased lipid peroxidation and ultimately the development of insulin resistance. (Savelieff et al. 2020) In another study the beneficial effects of T3s were observed for attenuation of inflammation and insulin resistance especially in overweight or obese women [4].

Around the Globe, management of diabetes mellitus is always a challenging task for the clinician. This is especially true to reduce the emergence of early complications. Therefore, the researchers are devoted to find the solution of this problem. In light of the delicacy of matter, a randomized control trial (RCT) was carried out in 2020, to assess a comparative efficacy of vitamins A, B, C, D&E supplementation on the antioxidant status and glycemic index of type 2 diabetes mellitus patients, The outcomes were measured and compared by various lab tests in pre and post supplementation period. The tests were malondialdehyde (MDA), changes in total antioxidant capacity (TAC), augmentation of glutathione peroxidase (GPx), enhance in superoxide dismutase enzyme (SOD), and thiobarbituric acid reactive substances (TBARS) and glucose levels. It was concluded that supplementation of vitamin E revealed highest antioxidant efficacy [5].

Rationale

The process of aging is a non-modifiable risk factor predisposing to many pathologies. The highlighted one includes hypertension, type II diabetes, hypercholesterolemia, cardiovascular morbidities, and many other degenerative changes. The allopathic medicines impart great significance to address these issues. But besides beneficial effects, many side effects used to be there. Therefore, even with advancement in medical science, there is emergence for a necessity of herbal remedies or plant-based natural compounds. So alternative form of treatment search is being carried out Globally. The aim behind the current systematic review is to add up the knowledge for the efficacy of tocotreinol and tocopherol for managing a patient of diabetes with or without insulin resistance. This will be a step forward to reduce the sufferings and miseries of diabetic patients.

Methodology

This systematic review was carried out by following PRISMA protocol and PRISMA guidelines – 2019 [6]. Figure 1 shows the PRISMA flow diagram for the selected 05 (N) articles for current systematic review. Four steps were followed for final inclusion of 05(N) articles i.e identification, screening, eligibility and finally included ones. For identification, records of 86(n) articles were identified by thorough search from various database. Sixty from PUBMED, 01(n) from Cochrane data base, 05(n) from Google scholar, 15 (n) from open Google search, 01(n) from PakMedinet, 01(n) from EMBASSE,01(n) from MEDLINE and zero form Cross Ref. Additional records identified through other sources by snowball effect from meta-analysis (n = 04), all from Pubmed , by snow ball method from a meta-analysis. Duplicate data was removed, and 15(n) articles were dropped. Screening was done for remaining 71(n) articles. Sixty-one articles were excluded due to various reasons and only 10(n) were found eligible. Amongst them 05(n) were excluded and only 05(N) were finally included for the current systematic review. The data was searched between the years 2021 to 2003. The details are shown in Figure I.

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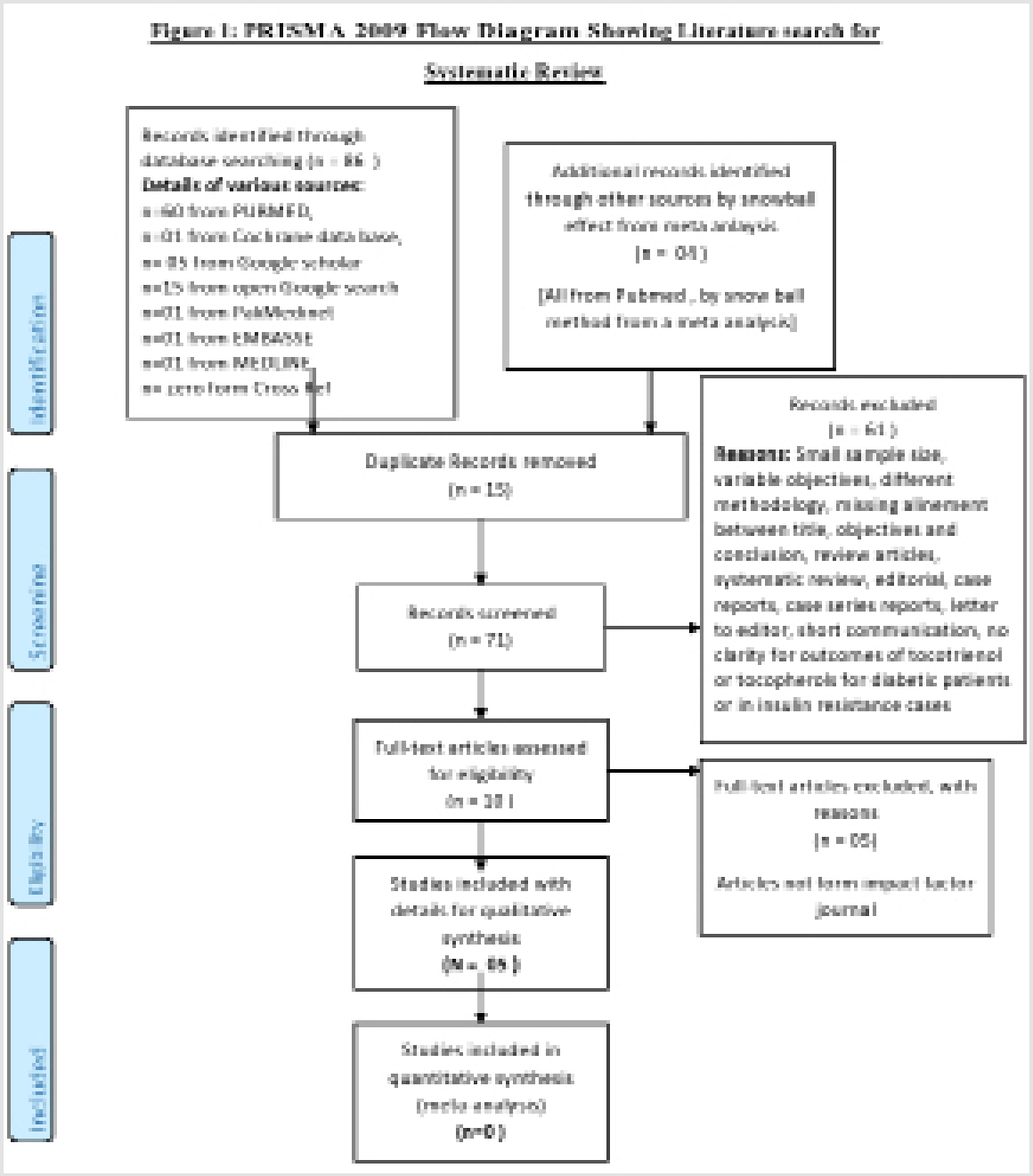

Figure 1: PRISMA 2009 Flow Diagram Showing Literature search for Systematic Review.

To ensure selection of authentic information certain MESH key words/synonyms were used for searching the relevant literature review. The selected key words were diabetes, vitamin E, tocotrienol, tocopherol, effectiveness, insulin resistance, diabetic nephropathy, diabetic neuropathy, diabetes complications. The inclusion criteria of study were the studies related to the use of vitamin E, tocotrienol, tocopherol, or their comparative efficacy in diabetic patients with or without insulin resistance. Studies having details of either the administration of any of four chemical forms of vitamin E i.e alpha-, beta-, gamma-, and delta-tocopherol and alpha-, beta-, gamma-, and delta-tocotrienol were included. Diabetic patient of any age bracket and of either type I or type II were enrolled for current systematic review. Besides this meta-analysis, systematic review, randomized control trials, original articles, and guidelines published in impact factor journals in last 05 years were also included.

While exclusion criteria were the editorials, letter to editor, case reports, commentary, case series report and short communications. The animal studies, ecological studies, RCTs without having placebo or control group were also excluded.

Results

The salient results extracted from the appraisal of 05 selected articles are shown in Table IA. By following PRISMA guidelines and based upon the inclusion and exclusion criteria of study, 05(N) articles were short listed. The standardization of data was done by following critical appraisal skill program (CASP) checklist. Amongst 05 (N) selected articles, 04(n) were the randomized control trials and one was original research article. All of these 04(n) were the registered ones having details for registration bodies and numbers, It is incorporated in Table IA.

Table 1.

Harvard Style for References	Type of study	Research questions	Objectives	Trial Regist No.	Study design & Sampling technique/ sample size	Method-ology	Conclusion	Limitation	Reason for selection
1. Tan GCJ. et al. (2019) [7]	RCT	Is Toco-trienol rich vitamin E, as Tocovid, has been shown to reduce oxidative stress and inflammation to ameliorate diabetes	To see the efficacy of Tocotrienol-rich vitamin E, for reducing oxidative stress and inflammation to manage diabetes	ANZCTR identifier: ACTRN12619001568101	Multicenter, double-blinded, placebo-controlled clinical trial, N=54	Estimation of following: · BSF, HbA1c, · serum creatinine, · eGFR, · urine albumin:creatinine · malondialdehyde, TNF-1, · VCAM-1, · Tx-B2.	Tocovid has been shown to attenuate the progression of DN and end stage renal disease, as assessed by serum creatinine and eGFR	Tocotrienol measurements were not accurate for patients who took Tocovid the night prior to scheduled visits, plasma tocotrienol concentrations were nearly undetectable	a. RCT b. Efficacy of Tocovid was studied for diabetic nephropathy c. Multi centered study
2. Ng YT et al. (2020) [5]	RCT	-	To evaluate the effects of Tocovid on nerve conduction parameters and serum biomarkers among diabetic patients.	· AC-TRN12619001568101, Australlia · NMRR-18-3928-45140. Malaysia	Multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial was conducted N= 80	Estimation of following: ·Nerve conduction study, ·Biomarkers NGF, ·malondialdehyde, ·TNF-1, ·VCAM-1, · Tx-B2.	Tocovid could be a disease-modifying agent targeting serum NGF to improve nerve conduction velocities in diabetic patients	The definite pharmacodynamics of tocotrienol-rich vitamin E were not studied	a. RCT b. Evaluation for the effects of Tocovid on nerve conduction parameters and serum biomarkers among diabetic patients were assessed c. Trial registered in Australlia & Malaysia

Despite thorough search from 08 search engines and >86 articles, no data was available showing comparative analysis for tocotrienol and a tocopherol on diabetes patients especially insulin resistance cases. Moreover no data was available for identifying the efficacy of tocopherol for diabetes. Therefore, this became a big limitation of study. Only 01(n) original article which is included as well had shown efficacy of tocotrienol for diabetic patients with insulin resistance. The research question was only available for 01(n) RCT. The objectives of most of these RCTs were to evaluate the effects of high dose tocotrienol in disease outcome in diabetic patients. Maximum follow up time was <03 months. For all RCTs, the base line labs were done at the beginning of study. Upon completion, they were repeated for comparison. The lab investigations included fasting blood sugar, HbA1c, liver function tests, renal function tests, urine albumin creatinine ratio, e GFR, malondialdehye, thromboxane A2 (TXA2), Vascular cell adhesion molecule (VCAM), advanced cell glycation end product (AGE), soluble receptor for AGEs(sRAGE), Nε-Carboxy-methyllysine (Nε-CML), Cystatin C, α-tocopherol concentration and insulin concentration by HPLC and ELISA.

The conclusion of all 05 articles was in line with the objectives and titles showing significant efficacy of tocotrienol for diabetes management. The ethical issues, consent details, funding sources, conflicts of interests, acknowledgements and authors contribution were mentioned in every selected article.

Discussion

After a thorough search, it was assessed that tocotrienols have antioxidant and anti-inflammatory properties. Due to which they are strongly recommended to be a part of diabetes management in view to reduce the serious complications of disease. The supplementation of vitamin E had proven to be beneficial for delaying the course of illness in diabetic patients. But the dose variation and hence accurate dosage identification is yet to be discovered.

Diabetes mellitus (DM) is a chronic metabolic disorder, which might have genetic and environmental factors as predisposition. (Study et al., 2020) It involves about 425 million people Globally. It is expected to be increased to 629 million by the year 2045. Therefore, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) came up with a consensus that management of type II diabetes mellitus (T2DM) should focus more on life-style modification along with use of vitamin and micro- nutrient supplementation. But this all should be in addition to the therapeutic management. The supported evidence is available and is proven from all 05(n) included studies that oxidative stress plays an important role in the pathogenesis and aggravation of DM. This is in line with the published literature which had shown the beneficial effects of using antioxidants specially to delay the occurrence of diabetes complications. The endothelial dysfunction is a main pathogenesis for macro and microvascular diseases such as retinopathy, nephropathy, lower extremity amputations, coronary artery and cardiovascular diseases. The scenario further worsens by the destructive properties of oxidative stress due to free radicals of oxygen and reactive oxygen species (ROS). This is the site of target for antioxidants like for currently extracted evidence and available literature. Antioxidants like tocotrienol helps their modification either enzymatically or non-enzymatically. 5 In one more study efficacy of tocopherol was mentioned as compared to tocotrienol. This is in view that it is the superior isoform of vitamin E. However, the further details were deficient in that particular study to justify this [7].

The pre and post lab investigations to compare disease outcome were done by various tests. They include fasting blood sugar, HbA1c, liver function tests, renal function tests, urine albumin creatinine ratio, e GFR, malondialdehye, thromboxane A2 (TXA2), Vascular cell adhesion molecule (VCAM), advanced cell glycation end product (AGE), soluble receptor for AGEs(sRAGE), Nε-Carboxy-methyllysine (Nε-CML), Cystatin C, α-tocopherol concentration and insulin concentration by HPLC and ELISA. This is in favour of many studies, which supports that diabetes complications can be evaluated by these mentioned predictors [7].

The source for tocotrienol-rich vitamin E also came under a debate. The one extracted from palm oil (Tocovid) was found to improve diabetes via its superior antioxidant, antihyperglycemic, and anti-inflammatory properties. In 04(n) studies for current systematic review, the extract of palm oil was used. Only one study, the source was a nut oil. This finding is supported by published data showing efficacy of Tocovid for diabetic nephropathy in patients with T2DM. The parameters used to assess this were HbA1c, blood pressure, Advanced Glycation Endproduct (AGE), soluble receptor for AGE (sRAGE), Nε-Carboxymethyllysine (Nε-CML), and Cystatin C. 5 Another study also supported the efficacious use of palm oil extracted Tocovid for diabetic peripheral neuropathy (DPN). This is due to its anti-inflammatory and anti fibrolytic property, which helps reduction of nerve growth factor (NGF). Thus, neuronal functions will be enhanced, ultimately improving nerve conduction velocities [8].

Amongst the predisposition of diabetes, obesity, chronic inflammation and increased oxidative stress are key factors to worsen the disease. They might trigger cells exposure to insulin resistance and pancreatic β-cell dysfunction. Tocotrienol, as a functional food component with anti-inflammatory, antioxidant, and cell signaling-mediating effects, can be a potential agent to supplement the management of obesity and diabetes. Tocotrienol also improve glucose homeostasis. The activation of peroxisome proliferator-activated receptors were the responsible one for these effects [9,10].

The analysis of all 05(N) articles showed a dose range between 200mg to 400mg for a period of maximum 8 – 12 weeks. The variation was there but the beneficial effects were observed in all included studies. The same is supported by available literature that ideal dose range should vary between 200-400mg. 11 The different finding was observed where duration of study was 24 weeks and 430mg olive oil extract as a source of totoctrienol was used and significant effects were observed to improve quality of life for diabetic patients [11,12].

Conclusion

Tocotreinol because of its antioxidant, anti-inflammatory and anti fibrolytic properties helps marinating the glycemic levels in diabetic patients. Besides this the emergence of diabetic complications was delayed. A clinical improvement in patients with diabetic nephropathy and neuropathy was seen as well. It was also observed that grape seed oil supplement of tocotrienol was proven beneficial as compared to sunflower oil supplement especially by lowering inflammatory markers.

Study Limitations

a) Despite thorough search from 08 search engines and >86 articles, no data was available showing comparative analysis for tocotrienol and a tocopherol on diabetic patients.

b) Moreover, no data was available showing comparative analysis for tocotrienol and a tocopherol on diabetic patients

c) Due to deficiency of original research articles, the currently included comparative literature is from only available review articles, regarding efficacy of tocotrienol and tocopherol.

d) No data was available for identifying the efficacy of tocopherol for diabetes.

e) There was no meta-analysis available, regarding the comparative efficacy of either the tocotrienol or tocopherol in diabetic patients Therefore no meta-analysis was included in the study.

f) Therefore, this became a big limitation of study and only included articles were focused for assessing efficacy of tocotrienol on diabetes.

Recommendations

1. Tocotrienol is found effective in managing the diabetic patients. So prospective randomized control trials (RCTs) over longer period should be carried out to study its beneficial effects

2. The currently available RCTs, have shown maximum follow up duration uptil 03 months.

3. The dose adjustment of tocotrienol needs to be calculated carefully in cases for follow up for more than 03 months.

4. In <03, high dose was given.

5. None of the available studies reported the side effects of tocotrienol. For longer duration follow up studies, it should be evaluated cautiously.

6. The efficacy of tocopherol needs to be explored for anti-diabetic effects

7. The comparative analysis of tocotrienol and tocopherol needs to be carried out for exploring anti diabetic effects.

8. Incorporation of tocotrienol as part of diabetic patients' management helps lowering the risk of diabetic nephropathy, diabetic neuropathy and end stage renal disease.

9. Comparative efficacy for grape seed supplement was proven beneficial as compared to sunflower oil supplement for diabetic patient management.

References

1. Szewczyk K, Chojnacka A, Górnicka M (2021) Tocopherols and tocotrienols-bioactive dietary compounds; what is certain, what is doubt?. Int J Mol Sci 22(12): 6222.
2. Koay YY (2021) A phase iib randomized controlled trial investigating the effects of tocotrienol-rich vitamin e on diabetic kidney disease. Nutrients 13(1): 1-16.
3. Soiza RL, Donaldson AIC, Myint PK (2018) Vaccine against arteriosclerosis: an update. Ther Adv Vaccines 9(6): 259-261.
4. Zhao L, Xiefan Fang, Maurice R. Marshall, Soonkyu Chung (2016) Regulation of obesity and metabolic complications by gamma and delta tocotrienols. Molecules 21(3): 234.
5. Ng YT, Phang SCW, Tna GCJ (2020) The E ff ects of Tocotrienol-Rich Vitamin E (Tocovid) Controlled Trial', Nutrients 12(5): 1522.
6. (2021) PRISMA-P-checklist.
7. Tan GCJ (2019) Tocotrienol-rich vitamin E improves diabetic nephropathy and persists 6–9 months after washout: a phase IIa randomized controlled trial. Ther Advan Endocrinol Metabol 10: 1-16.
8. Tan SMQ (2018) Tocotrienol-rich vitamin E from palm oil (Tocovid) and its effects in diabetes and diabetic nephropathy: A pilot phase II clinical trial. Nutrients 10(9): 1315.
9. Chu GHL, Phang W (2020) Vitamin E Levels in Ethnic Communities in Malaysia and Its Relation to Glucose Tolerance, Insulin Resistance and Advanced Glycation End Products: A Cross-Sectional Study. Nutrients 12(12): 3659.
10. Aryaie A (2020) Actions of annatto-extracted tocotrienol supplementation on obese postmenopausal women: Study protocol for a double-blinded, placebo-controlled, randomised trial. BMJ Open 10(3): 1-9.
11. Koay YY (2021) A phase iib randomized controlled trial investigating the effects of tocotrienol-rich vitamin e on diabetic kidney disease. Nutrients 13(1): 1-16.
12. Pang KL, Chin KY (2019) The role of tocotrienol in protecting against metabolic diseases', Molecules 24(5): 923-924.

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