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REVIEW ON QUERCETIN: A WONDER BIOFLAVONOID WITH THERAPEUTIC POTENTIAL

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ABSTRACT

The use of medicinal plants is becoming increasingly important in the creation of new drugs. Herbal drugs are well-liked due to their effectiveness, safety, and lack of adverse effects. Different degrees of success have been achieved in the treatment and prevention of diseases using plants and plant products. Nowadays, natural products made from plants are highly sought after in many countries worldwide. As the description above shows, nature is the best combinatorial chemistry and contains likely solutions to every human illness. Medicinal plants must be used to treat stone ailments. Herbal remedies have previously gained popularity due to the drawbacks of contemporary therapy. By proving the safer indigenous system's effectiveness in treating a variety of illnesses, it is vital to increase public acceptance and awareness. Let's hope that natural products will be able to compete with modern medications in the future by offering further advantages like lower costs and improved safety. The majority of people on the planet currently lack access to contemporary medical facilities for the treatment of urinary stones due to socioeconomic conditions. Therefore, more clinical research is required to validate the traditional antiurolithiatic claims made by these plants and herbal combinations, in addition to chemical characterization of antiurolithiatic herbs. This review illustrates the adaptability of quercetin in a variety of formulations.

KEYWORDS: Quercetin, kidney stone, Calcium oxalate, Moringa oleifer.

INTRODUCTION

The concentration of minerals from urine causes a solid mass called a kidney stone to form in the kidneys. Around 80% of kidney stones are calcium-containing stones, which are the most prevalent kind. These stones usually contain calcium oxalate (CaOx), either by itself or in conjunction with calcium phosphate. A calcium oxalate stone can be either calcium oxalate monohydrate (COM) or calcium oxalate dihydrate (COD).[1] Nephrolithiasis, or kidney stones, is becoming more common worldwide, particularly in women and as people age. Chronic renal illness has been linked to kidney stones.[2] A high intake of calcium from the diet is more likely to increase the risk of kidney stones. Patients who have calcium-containing stones are therefore frequently recommended to reduce their calcium consumption.[3]

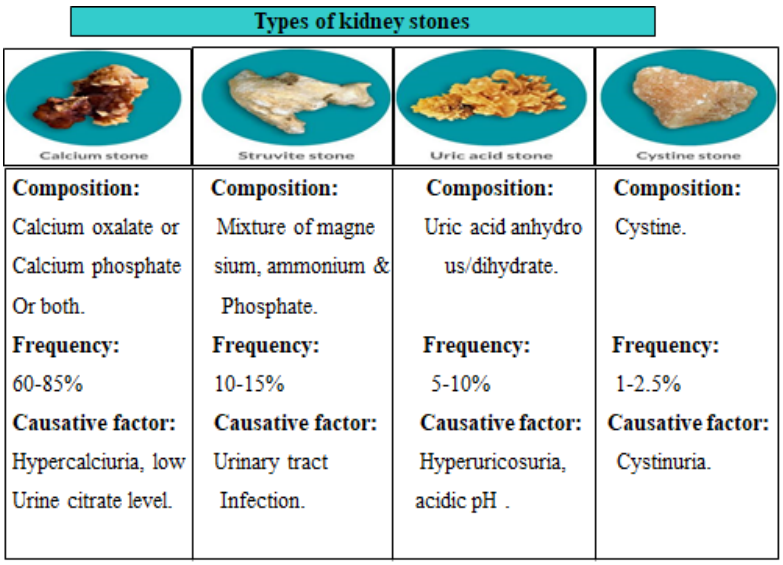

Fig 1: Types of kidney stones.[4]

Moringa oleifera is a plant belonging to the Moringaceae (drumstick family), which has worldwide distribution. Local people know it as senjana (Hindi), Nugge/Guggala(Kannada), Murungai (Tamil), Mochakamu (Telugu), Shevga (Marathi), Shigru (Sanskrit), Drumstick tree, or Horseradish tree (English). It has been determined that M. oleifera is a rich source of minerals, tocopherols, carotenoids, polyunsaturated fatty acids, ascorbic acid, folate, phenolics and glucosinolates. Due to its high concentration of monounsaturated fatty acids in the form of oleic acid, moringa seed oil, sometimes referred to as “Ben oil”, is used to produce biodiesel. The many therapeutic benefits of Moringa oleifera have also long been recognised in ayurvedic and unani medicinal systems. The therapeutic qualities and pharmacological activities, such as antihypertensive, diuretic and cholesterol-lowering activities, antispasmodic, hepatoprotective activity, antibacterial and antifungal activity,

antitumour and anticancer activities, and thyroid hormone regulation.[5] The clinically confirmed effects of herbal medications, such as immunomodulation, adaptogenicity, and antimutagenicity, have sparked public interest. People are turning to nature for safe solutions because excessive use of synthetic medications increases the risk of severe drug reactions.[6]

Plant Profile of Moringa oleifera

The common names for Moringa oleifera include horseradish tree and drumstick tree. It is utilised as a vegetable and to treat a number of ailments in Indian traditional medicine.[7] It is widely grown close to homes in Bengal, India, and Assam. Additionally, it is grown across the West Indies, southern Florida, Central and South America from Mexico to Peru, Brazil, northeastern Pakistan, northeastern Bangladesh, Sri Lanka, West Asia, East and West Africa, and more.[8]

Botanical Description of moringa oleifera

➢ Kingdom	Plantae
➢ Sub kingdom	Tracheobionta
➢ English	Drumstick tree
➢ Division	Magnoliophyta
➢ Class	Magnoliopsida
➢ Family	Moringceae
➢ Genus	Moringa
➢ Species	Oleifera

Synonyms

Table no 1: Different names in different language of moringa oleifera.[9]

Latin	Moringa oleifera
Sanskrit	Subhanjana
Hindi	Saguna, Sainjna
English	Drumstick tree, Horseradish tree, Ben tree

Phytochemical composition of moringa oleifera

Siddha, Ayurveda, Yoga, Unani, Homoeopathy, and Naturopathy, with the exception of

allopathic. Among India's 1.1 billion people, almost 70% still practise these non-allopathic medical systems.[10] Moringa oleifera powder phytochemical analyses of its polyphenols, including rutin, kaempferol glycosides, 43.75% quercetin glucosides, and chlorogenic acids, using high-performance liquid chromatography.[11] The aqueous extracts of Moringa oleifera leaves, fruits, and seeds included gallic acid, chlorogenic acid, ellagic acid, ferulic acid, kaempferol, quercetin, and vanillin. All of the chemicals were examined using HPLC methods.[12] The presence of flavonoids such as kaempferol, quercetin, and rutin, as well as phenolic acids such as gallic acid, chlorogenic acid, ellagic acid, and ferulic acid, using HPLC techniques.[13]

Traditional Uses

- Traditional uses of the plant include diuretics, expectorants, stimulants, and antispasmodics. The new root has internal uses as an antilithic, diuretic, and stimulant.
- Seeds are stimulating and abrasive.
- Bark has emmenagogue properties. Antifungal, antimicrobial, and even abortifacient. Flowers have cholesterol-boosting, bile-stimulating, tonic, and diuretic properties.
- Root juice is used in antiepileptic and heart tonic products. Asthma, enlarged liver and spleen, deep-seated inflammation, neurological debility, and diuretic.
- Root bark has antiviral, anti-inflammatory, and analgesic properties. The flowers and stem bark have a hypoglycemic effect. Seed infusion has anti-inflammatory, antispasmodic, and diuretic properties; it is also used to treat sexual illnesses.[14]

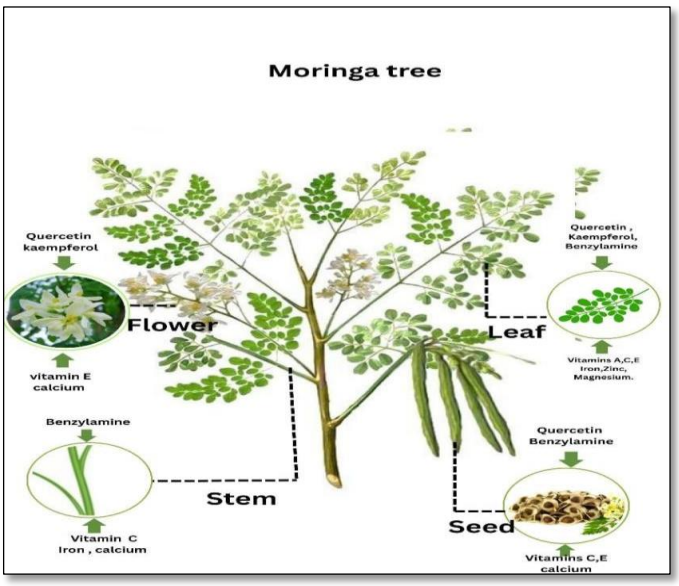

Fig. 2: Moringa tree.

Extraction method

Maceration technique

A conical flask was filled with 500 mL of 70% ethanol and 50 g of powdered moringa leaves. For a whole day, the mixture is stored in a dry, dark place with sporadic shaking. The extracts were centrifuged after a day, and the supernatant was gathered. In vacuo, the filtrate was concentrated. After concentration, the extract was freeze-dried and kept in a refrigerator for additional examination.

Soxhlet method

The extraction chamber was filled with a porous thimble containing 50 g of powdered material. The boiling flask was filled with 500 mL of 70% ethanol and heated to 40ºC for 16 hours, or eight syphons. The extract is concentrated using a vacuum rotary evaporator after 16 hours of extraction. Concentrated extracts were obtained, freeze-dried, and kept at -4ºC.

Phytochemical screening of moringa extract

Alkaloids, flavonoids, steroids, reducing sugar, tannins, and saponins were qualitatively detected through phytochemical analysis of moringa leaf extract.

Alkaloids: A few drops of diluted iodine solution, or Wagner's reagent, were added to the Moringa leaf extract. The development of a reddish-brown hue indicated that alkaloids were present.

Flavonoids: 10 mL of distilled water and 3 mL of moringa leaf extract were combined, and the mixture was vortexed with a few drops of magnesium. The presence of flavonoid was confirmed with the observance of a yellowish color with the addition of concentrated hydrochloric acid.

Saponins: After diluting 3 mL of moringa leaf extract with 2 mL of distilled water, the extract was heated and vortexed. When froth formed, the presence of saponins was verified.[15]

Standerdization of Moringa Extract

Standerdization of Quercetin Using UV Spectroscopy

I. Preparation of quercetin standard curve

The maximum wavelength must be found in order to improve sensitivity and reduce errors in repeated measurements.[16] This study used a reference solution with a 100 ppm quercetin concentration to determine the maximum wavelength, which was measured using UV-Vis

spectrophotometry in the 200–800 nm wavelength range. The wavelengths of visible and sister UV rays ranged from 200 to 800 nm; thus, measurements were made at that range. Two-peak spectra at 210 nm and 361.8 nm were discovered to be the maximum wavelength based on optimisation screening findings. The maximal absorption of ethanol as a solvent is reported to occur at 210 nm.[17] Thus, it may be said that quercetin's maximum wavelength was 361.8 nm. However, more research revealed that quercetin's maximum wavelength is 380 nm.[18] A quercetin standard solution with a series of concentrations of 4 ppm, 6 ppm, 8 ppm, 10 ppm, and 12 ppm was used to create a standard curve. The researchers could determine the quaternary levels of quercetin in the tamarind leaf extract after creating linear regression line equations from the absorbance data of each concentration series. The linear regression line equation developed from the quercetin standard curve was y = 0.0616x 0.018, with the intercept axis value of 0.0616 and the slope value of -0.018.[19]

Standerdization of Quercetin Using HPTLC

I. Standard Stock Solution and Sample Preparation

Standard stock solutions containing 1 mg/mL of quercetin, rutin and coumaric acid were prepared in methanol and filtered through 0.45 lm (Millipore) filters for calibration studies. A sample was prepared from dried and powdered flowers (1 g) of R. arboreum. The powder was extracted with methanol (4 · 10 mL) at ambient temperature for 16–20 h, filtered and concentrated under vacuum to obtain the crude extract. A known amount of extract (20 mg) was taken and dissolved in methanol (1 mL) and filtered through a 0.45 lm filter for HPTLC analysis.

II. HPTLC Instrumentation

A Camag HPTLC system equipped with an automatic TLC sampler, TLC scanner 3 with UV cabinet and twin trough glass tank was used for the analysis. The samples were applied using an automated TLC sampler in 6 mm bands at 10 mm from the bottom, both sides and 6 mm space between the two bands.

III. Calibration and Quantification

Standard stock solutions of quercetin, rutin and coumaric acid (1 mg/mL) were diluted in methanol to obtain the working solutions of concentration 0.05 mg/mL for quercetin and rutin and 0.025 mg/mL for coumaric acid. The obtained working standard solutions were then applied on the RP-TLC plate for preparing four-point linear calibration curves. Quercetin and rutin were spotted at 10, 20, 30, and 40 µL, while coumaric acid was spotted at 8, 16, 24, and

32 µL, respectively. 25 mL of sample solution (20 mg/mL) was taken and applied on the RP-TLC plate in triplicate with a similar band pattern. The experimental parameters were identical for all the above analyses.[20]

Quercetin Solubility Profile

Solubilization of quercetin in water

When quercetin is neutral, it dissolves very weakly in water. When quercetin deprotonates, the medium's pH rises, making it more and more negatively charged and increasing its water solubility. On the other hand, oxidation processes that cause quercetin to chemically change into smaller byproducts are likewise favoured by negative charges. Although this can easily be followed by tracking changes in quercetin's UV spectra as the pH rises, this is far more complicated than the straightforward redshift that deprotonation is supposed to produce. Thus, it is difficult to track quercetin's rise in water solubility without causing oxidative destruction, and the two phenomena overlap. Consequently, assessed quercetin's solubility in water as a function of pH.[21]

Solubility Study in Blends

In comparison to other mixes, the A4 blend showed a greater solubility enhancement. These findings proved the mixed solvency concept, which states that water-soluble materials, such as hydrotropes, co-solvents, and water-soluble solids, can be blended at random to give water- insoluble medications the solubility they want. However, raising the concentration of solubilisers not only makes quercetin more soluble but also increases the toxic effects of each solubiliser alone. Consequently, blends of solubilisers can be used in the formulation of liquid dosage forms to provide concentrated solutions at a safe level and to lessen the toxicity of solubility.

Querectin in different solubilizers

Table no. 2: Quercetin in different solubilisers.[22]

Solvents	Solubility
40%w/v Sodium citrate	38.24
40%w/v Sodium acetate	37.66
40%w/v Urea	14.223
40% w/v Propylene glycol	5.867
40% w/v Glycerin	5.923
40%w/v PEG 200	2.362
40%w/VPEG 400	2.503
40%w/v PEG 600	3.5144

40%w/v PEG 4000	2.826
40% /V PEG 6000	5.57

Application Of Quercetin In Severe Diseases

1. Cancer

Strong flavonoid quercetin has been shown to have chemoprotective effects in a number of in vitro and in vivo settings. It is a dependable molecule in cancer treatment because of its many anti-cancerous qualities, which include decreased proliferation, the capacity to induce apoptosis, suppression of mitotic processes, and cell cycle arrest.[23] Despite having low bioavailability, poor permeability, and poor solubility, quercetin can be a powerful treatment. When taken in the right dosage, quercetin is non-toxic and inhibits the growth of tumours. Numerous investigations conducted both in vitro and in vivo demonstrate that quercetin controls the cell cycle, prevents metastasis, and encourages apoptosis. It is also known that quercetin prevents the production of metabolites of polyunsaturated fatty acids, which are linked to the development of cancer. It suppresses "lipoxygenase", the enzyme that breaks down polyunsaturated fatty acids (PUFA). In the treatment of persistent prostate cancer, quercetin's effects were noted. As a result, quercetin by itself or in combination can be employed as a cancer treatment.[24] In colorectal cancer, quercetin demonstrates its chemoprotective properties by stopping the cell cycle, altering oestrogen receptors, and controlling signalling pathways.[25]

2. Anti-Alzheimer Activity

This protects against the neurodegenerative processes that lead to AD and helps against oxidative stress. Quercetin lessens the negative consequences of chronic inflammation in the brain by preventing microglial cell activation and lowering the synthesis of proinflammatory cytokines. In general, quercetin may reduce oxidative stress and modulate neuroinflammation to provide its anti-Alzheimer actions. Verbal, olfactory, episodic, and visual memory are among the various types. Implicit (nonverbal habitual memory) and explicit (active or passive recollection of facts) are the two categories into which they fall. This helps prevent oxidative stress and guards against the neurodegenerative processes that cause AD. By inhibiting the activation of microglial cells and reducing the production of pro-inflammatory cytokines, quercetin reduces the detrimental effects of chronic inflammation in the brain. Quercetin's anti- Alzheimer effects may generally be attributed to its ability to control neuroinflammation and reduce oxidative stress. These include visual, verbal, olfactory, and episodic memory. They fall into two categories: explicit (active or passive recollection of facts) and implicit

(nonverbal habitual memory).[26,27]

3. Urolithiatic Activity

Dietary polyphenols have a good effect on human health and may be used as preventative measures for several diseases, according to a wealth of experimental research. Eating foods high in polyphenols, such as quercetin, epigallocatechin-3-gallate, resveratrol, and others discussed in this review, has been shown to reduce the risk of a number of chronic illnesses, including diabetes mellitus, neoplasms, neurodegenerative diseases, chronic inflammatory disorders, and cardiovascular pathologic conditions. Research from both clinical and experimental investigations shows that eating a diet high in polyphenols may help prevent and treat these illnesses.[28,29]

To differentiate the pleiotropic effects of polyphenols from their direct nephroprotective properties, we have compiled the most recent information on the underlying mechanisms of antilithiatic and protective properties of polyphenols in nephrolithiasis as established by in vitro studies.[30]

Outcomes: Oral administration of alcoholic Moringa extract at a dose of 250 mg/kg body weight significantly protected the rabbits' kidneys against contrast-induced damage by raising GSH levels and lowering MDA levels. According to the histological data, the extract activities also prevent kidney damage caused by the contrast, which is characterised by glomerular tuft congestion, increased Bowman's Space, atrophy of the glomerulus, and degeneration of certain tubules. According to this study, the alcoholic extract of moringa improves oxidative stress defence against kidney damage.[31]

QUERCETIN LIPID-BASED FORMULATIONS

There is growing evidence that quercetin, one of the significant bioflavonoids found naturally in plants, has a variety of uses and can work as a multipurpose medication.

Solid-lipid microparticles, solid-lipid nanoparticles (SLN), nanostructured-lipid carriers (NLC), nanoemulsions, microemulsions, liposomes, niosomes, phytosomes, and transferosomes are some of the novel formulations of quercetin that have been developed. It has been discovered that these formulations exhibit superior efficacy, stability, and a variety of therapeutic actions in comparison to traditional quercetin formulations.

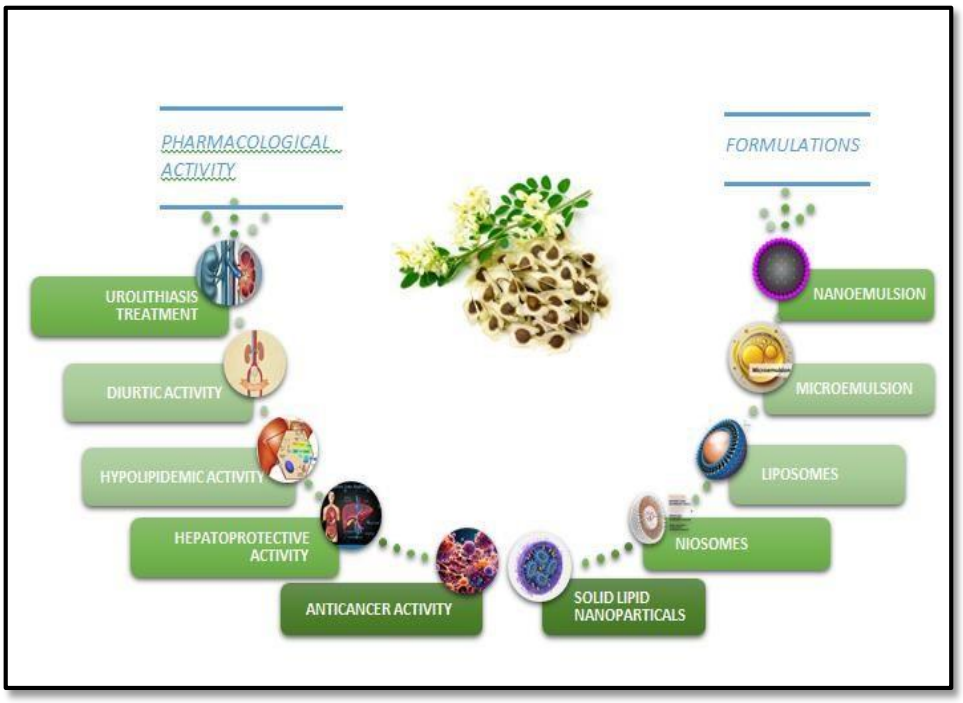

Fig. 3: Quercetin related formulation & diseases.

Quercetin Lipid particulate system containing formulation

Solid Lipid Nanoparticle (SLN)

The lipid nanocarriers of the first generation are called SLNs. These were created to synthesise drugs in solid lipids, ideally using a cold or hot homogenisation process, depending on the drug's thermal stability. To increase quercetin's cellular penetration and target hepatocellular carcinoma cells, researchers created an SLN formulation of quercetin that contains cholesterol or phytosterol. HepG2 cells were used in the MIT assay to assess quercetin-SLN's cytotoxicity. The benefits of SLN over other traditional colloidal drug delivery methods, including its solubility, toxicity, biocompatibility, efficiency, and ability to shield active ingredients from deterioration. Using the emulsification solvent evaporation process, 23 distinct formulations of SLN loaded with quercetin were made.[32]

Emulsion systems containing quercetin formulations

Microemulsion

Quercetin-loaded microemulsion formulation intended to treat brain tumours through the intranasal pathway. A neurotherapeutic agent could be directly delivered to the nose and then to the brain through intranasal drug administration, which circumvents the blood-brain barrier and trigeminal nerve pathways. Quercetin has the potential to prevent angiogenesis, which is the process by which new blood cells are formed in blood arteries that support the growth of

tumours. Using a spontaneous emulsification process, quercetin microemulsions were created by gradually adding a mixture of oil, surfactant, and co-surfactant. Therefore, it was determined that an intranasal delivery of a drug-loaded quercetin microemulsion can be a very promising and successful method for administering an anticancer agent for the treatment of a brain tumour.[33]

Vesicular systems containing quercetin formulations

Liposomes

According to studies, researchers synthesised quercetin-copper-based liposomal formulations and investigated the therapeutic potential of quercetin. They describe the need to increase quercetin's solubility and the various formulation strategies that have been used to create more water-soluble pro-quercetin compounds that biologically convert to quercetin, as well as the use of liposomes, polymers, or milling to create nanocrystals. This study demonstrates that a copper- quercetin liposomal formulation is appropriate for intravenous administration and that the resulting formulation increases the apparent solubility of quercetin by at least 100 times. The authors noted that the new liposome technology with encapsulated copper in quercetin was very effective and that the liposomal formulations of quercetin frequently exhibit lower rates of elimination from the plasma compartment and increased blood circulation when compared to native quercetin. The new copper-based liposomal formulations produced quercetin formulations that are more stable and reliable. These formulations also have the added benefit of liposomes' propensity to extend the half-life of an associated anticancer medication. Research on quercetin and its significance as a component of cancer treatment combinations has been ongoing.[34]

CONCLUSION

Medicinal plants are becoming extremely significant in the development of novel medications. Herbal medications are popular because of their safety, efficacy, and lack of side effects. Plants and plant products have been used to treat and prevent diseases with varied degrees of success. Natural plant-derived goods are currently in high demand in many nations throughout the world. Nature is the best combinatorial chemistry and has probable answers to all diseases for mankind, as evidenced by the preceding explanation. Stone illnesses necessitate the use of medicinal plants. People's attention has already been drawn to herbal treatments as a result of the negative effects of modern medicine. To improve public acceptance and knowledge, it is critical to build trust and faith in the safer indigenous system by demonstrating its efficacy in

the treatment of various diseases. Let us hope that in the future, natural goods will be able to compete with contemporary pharmaceuticals, providing additional benefits such as increased safety and reduced costs. Due to socioeconomic circumstances, the majority of the world's population is now unable to access modern health care facilities for the treatment of urinary stones. Therefore, in addition to chemical characterisation of antiurolithiatic herbs, more clinical research is needed to support traditional antiurolithiatic claims made by these plants and herbal combinations. Different formulations are included in this review that shows the versatility of quercetin in various formulations.

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against Alzheimer's disease.