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Brief Review

Uses of Naringenin in Major Diseases: A Brief Review

Mohammad Hossein Karami[1,2]*, Majid Abdouss[1] and Behzad Aghabarari[2]

[1]*Department of Chemistry, Amirkabir University of Technology, P.O. Box 15875-4413, Tehran, Iran*

[2]*Nanotechnology and Advanced Materials Department, Materials and Energy Research Center, Karaj 31787-316, Iran*

***Corresponding author**

Mohammad Hossein Karami, Department of Chemistry, Amirkabir University of Technology, Iran

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Abstract

Naringenin (NRG) is a chemical found in citrus fruits like oranges and lemons, as well as in some other fruits like bergamot, tomatoes, cocoa, and cherries. It is a type of chemical called flavanones. NRG can help fight cancer, reduce swelling, and protect the body from harmful substances. Extensive research has been done over the past few decades, showing a detailed picture of many different plant chemicals and how they could be used for medical purposes. These natural compounds are important for medical use and are made up of polyphenols, followed by terpenoids and alkaloids. Many research studies have shown that phytochemicals play a key role in providing health benefits against different diseases. Not all plant chemicals have strong healing powers, and only some of them show important health effects. Naringenin is a compound in oranges and lemons that can make your immune system stronger, fix damaged DNA, and get rid of harmful molecules in your body. Although naringenin has limited availability in the body, it is known for its various healing properties, including reducing inflammation and acting as an antioxidant. This study looks at how naringenin can be helpful in treating important diseases because of its antioxidant properties.

INTRODUCTION

Flavonoids are natural compounds present in plants, herbs, and beverages, with a wide variety of over 4000 types. Naringenin (NRG), a specific type known as a flavanone, was first identified in 1907 as a chalcone by Control and Tutin [1]. Despite its ability to dissolve in alcohol and exist in various forms like NRG or glycosidic shape, the body's poor absorption of NRG due to its limited water solubility has posed challenges in practical use. Efforts have been made to enhance NRG's bioavailability, including the development of carriers for controlled release and targeted delivery to specific organs or tissues, thereby increasing effectiveness while minimizing undesired side effects [2]. These specialized carriers, encapsulating plant compounds like NRG or naringin, facilitate improved solubility in water, better bioavailability, and enhanced therapeutic efficacy, ultimately reducing the required dosage of medication [3-5].

The US Food and Drug Administration has approved several new drugs made from traditional herbs to help prevent and treat cancer. It is crucial to discover new, effective anti-cancer drugs found in natural plants. Research from various sources, such as books and scientific journals, has shown that natural remedies derived from plants can combat certain types of cancer and have been approved for medical use [6]. Medicines obtained from ancient medicinal plants have proven to be effective in fighting cancer. Phytochemicals, especially flavonoids, play a significant role in cancer treatment and offer many health benefits. Flavonoids are heat-stable natural products commonly found in herbs, vegetables, tea, and alcohol. They are classified into nine groups: flavones, flavonols, flavan-3-ols, flavanones, auronon, chalcones, isoflavones, proanthocyanidins, and anthocyanins [7]. Citrus, an Indian medicinal plant, has numerous health benefits. Naringin, a flavanone glycoside found in citrus fruits, is a promising natural medicine. Studies suggest that naringin may help prevent the growth of certain types of cancer, including esophageal, stomach, colon, and ovarian cancer [8]. However, naringin has limitations such as low absorption in the body, rapid decomposition in acidic environments, and lack of specificity in targeting areas. New drug delivery methods utilizing nanoparticles are being explored to address these limitations and enhance drug safety, representing a step forward in the field. This article examines a novel approach to cancer treatment using nanoparticles to deliver naringin [9].

This study delves into the therapeutic applications of NRG, emphasizing its antioxidant properties and substantial potential in the treatment of various significant diseases. In this research, the study focuses on analyzing the important properties of NRG (Figure1).

The patent standing of naringin for its potential in treating cancer

Phytochemicals are a very intriguing subject within the field

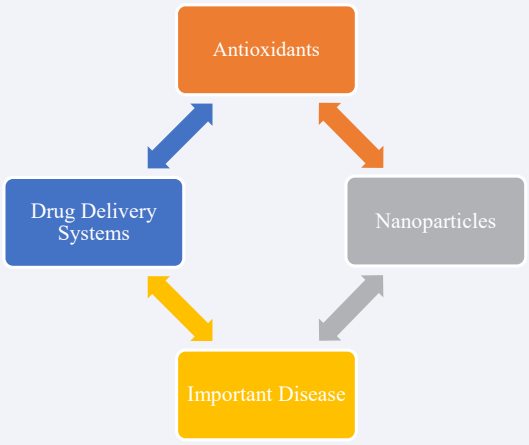

Figure 1 The important points in the properties of naringenin.

of developing modern products. There is a high demand for plant chemicals, as evidenced by research conducted worldwide. Of particular interest are new naringin compounds and drugs that can combat cancer without causing any side effects (Table 1) [10-14].

CANCER

NRG can help prevent and treat cancer in many different types of cells, like lung, colon, cervical, pancreatic, and skin cancer cells. NRG can cause cancer cells to die, make it harder for them to work, and stop them from multiplying [6]. NRG stops cancer-causing substances from working by using specific parts. One potential approach to potentially manage breast and prostate cancer involves upregulating specific proteins while inhibiting others. It also has the ability to stop cells from growing and spreading by lowering certain substances in the body [7]. NRG stops cyclin and cyclin-dependent kinase from working, which helps to control leukemia. NRG also slows down the growth of blood vessels, which helps to reduce the spread of cancer. Many different types of tiny drug delivery systems made from materials like PLGA, carbon nanotubes, silk, and others have been used in studies [8]. A novel approach was employed to enhance drug delivery efficiency by utilizing a green nanohybrid hydrogel as a carrier system. This system was developed by blending L-Cysteine (CYS) with chitosan, with the addition of tiny zinc particles to enhance the interaction between the carrier and the medication [9]. The conjugation of CYS led to the structural modification, making it more adhesive and easier to disintegrate in bodily fluids, while also inhibiting certain proteins. Additionally, a material known as dialdehyde cellulose was utilized to produce a new type of gel through a polymeric process. This gel exhibited the capability to release 86.9 out of 100 parts of the NRG substance up to 72 times, with 78% release at a concentration of 1 milligram per milliliter. In experimental trials, this delivery system demonstrated effectiveness and safety on non-cancerous mouse cells. Furthermore, the smaller hydrogel exhibited increased cytotoxicity towards A431 skin cancer cells compared to free NRG when used for treatment [10].

Table 1: The patent standing of naringin for its potential in treating cancer.

Patent Number	Title of the Patent	Reference
EP0352147A2	Use naringine, naringenin, or their related substances in the production of an anti-cancer mixture	[10]
WO2017008769A1	Research on naringenin and naringin for the treatment of cancer using radiation therapy	[8]
WO1998016221A1	Naringin and naringenin are substances that can inhibit an enzyme called Hmg-CoA reductase	[11]
US5145839A	Medicine and how to use it	[12]
EP2163247B1	Using naringenin and naringin to inhibit the growth factor beta 1 signal pathway	[1-4]

A new method was utilized to improve NRG delivery by using a green nanohybrid hydrogel as the delivery system. This system was created by combining L-Cysteine (CYS) with chitosan, and then adding zinc oxide nanoparticles derived from plants to enhance the interactions between the carrier and the drug [11]. The CYS bonding allowed the system to adhere better to mucus, facilitate easier dissolution, and inhibit enzyme activity. Additionally, Dialdehyde Cellulose (DAC) was employed to link the polymeric matrix and form the green nanohybrid hydrogel. The new carrier was capable of retaining 86.09% of NRG and releasing up to 72.78% at a concentration of 1 mg/mL. Moreover, this system demonstrated compatibility with non-cancerous mouse cells in testing for effectiveness with living organisms. Conversely, the small mixed hydrogel exhibited greater toxicity (twice as much) when utilized. A comparison was made regarding the response of A431 human skin cancer cells to free NRG (Figure 2) [12].

BRAIN DISEASES

Diseases that affect the brain, like Alzheimer's and Parkinson's, are very important and can cause a lot of problems for people all over the world. Severe illnesses can greatly impact individuals, rendering them sick and unable to perform daily activities [11]. Ahmad and his team developed a special juice containing NRG to enhance its effectiveness in treating cerebral ischemia. The NRG-loaded nanoemulsion, designed as a gel, is administered intranasally and can change its shape in response to temperature variations. It solidifies at around 28-30 oC. The collected drops marked a size of about. 98.31 nm and a PDI about 0. 386. In another study, Shadab and his team. Linked the ability of NRG to

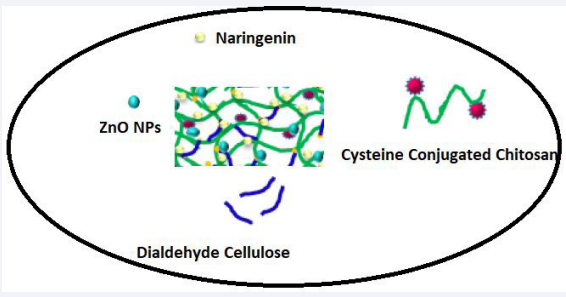

Figure 2 Naringenin is encased in a small hydrogel along with other materials (Nanohybrid hydrogel).

protect the brain and fight against harmful substances to treating PD. Damage from chemicals in the body has been linked to Parkinson's disease and is thought to be a main reason for it. This damage causes harm to the brain and leads to the death of nerve cells. NRG has properties that can protect the brain and act as an antioxidant, which is very important for treating Parkinson's disease [12-14]. NRG was put in positively charged chitosan particles (approximately measured). Around 88 nanometers, approximately. 031, positive charge ca. Made using the ionic gelation method, resulting in high NRG effectiveness (> 91%) and designed to deliver medicine from the nose to the brain. Another study looked at a way to deliver NRG through the nose using a combination of Vitamin E and other ingredients. Possible combined effects of the antioxidant effects of vitamin E and NRG were studied. The improved tiny oil droplets were about the size of a small bead. The size is 38 nanometers, the PDI is less than 0. 15 and the zeta potential is negative [15].

LIVER DISEASES

NRG could be a characteristic substance that has been studied a part for its capacity to assist with liver infections in a secure way. Liver maladies happen since of diverse things, like taking as well much medication, drinking liquor, not eating right, or getting infections [14] so, the things NRG does may well be exceptionally supportive in halting and treating liver maladies. NRG can halt the harm caused by oxygen within the body, Toll-Like Receptor (TLR), the Mitogen-Activated Protein Kinase (MAPK), and non-traditional TGF-β pathways [16]. NRG can help with non-alcoholic greasy liver infection by controlling how the body employments and breaks down fats and cholesterol. NRG has been looked at completely different ways utilizing liver injury substances like N-methyl-N-nitro-nitro guanidine, Lipopolysaccharide (LPS), or Carbon Tetrachloride (CCl4) in both live creatures and in test tubes. Examined how NRG can secure the liver from harm caused by CCl4 by giving it as a pill or in minor particles. The journalists gave the creatures the medication some time recently giving them the poison [17]. The journalists looked at blood levels of certain chemicals and measured the action of different substances in liver tissue.

The journalists appeared that utilizing particles can make NRG break up more effectively and help control how drugs are discharged. Giving the creatures the medication and the particles some time recently treatment brought down the levels of AST and ALT in their blood by 1-1 [18]. These proteins offer assistance to anticipate harm to the body's cells. 3 times more of it than when the medicate was utilized on its claim. Chen and his group examined how well NRG-filled liposomes worked on nonalcoholic greasy liver malady (NAFLD) in mice. The creators made NRG-filled liposomes, looked at how the NRG is discharged from them, and examined how the body forms it compared to when the drug is not in liposomes [19].

DIABETES

NRG helps to reduce blood sugar levels by stopping the body from holding onto sugar from food. NRG anti-diabetic medicine makes insulin work better, lowers sugar in blood, and decreases swelling in fat. It also affects certain proteins and enzymes in the body that are involved in controlling blood sugar. In a later study, Maity and Chakraborty made small particles with a drug using a special method [20]. The NRG connection was about 70%, and the particles were measured to be around 129 nanometers. Additionally, they looked at whether NRG-loaded PLGA nanoparticles could help with diabetes, compared to just using NRG by itself. They tested this in rats with diabetes caused by streptozotocin [21]. The researchers found that the rats who were treated with nanoparticles had lower levels of glycated hemoglobin, higher levels of stress, and improvements in cholesterol and oxidative stress. This was not seen in the rats who were treated with free NRG. Staying to bodily fluid and how well pharmaceutical comes off it changed with distinctive levels of corrosiveness [22]. The arranged nanoformulations gradually discharge vitality over time. In tests with living creatures, diabetic rats appeared lower blood sugar levels after taking NRG-loaded nanoparticles by mouth. In addition, tests on tissue and blood appeared that the little particles were within the mouth. The medicines did not cause any destructive impacts within the body [23].

INFLAMMATORY DISEASES

In the event of sickness or injury, macrophages release substances like cytokines, nitric oxide, and prostaglandins during the inflammatory process. Producing too many of these compounds can cause many long-lasting inflammatory diseases like asthma, heart disease, arthritis, lung scarring, joint pain, shock from infection, and cancer [24]. So, their control may be an important way to treat many ongoing inflammatory diseases. Kumar and Abraham planned to make a special kind of nanoparticle called PVP-coated NRG in this place [10-14]. The safety and effects on the immune system of these nanoparticles were studied in male rats. It was found that they are safe and can be used for medical purposes. They wanted to see if NRG can stop inflammation in mouse cells. In summary, the study showed that the NRG nanoparticle has the potential to reduce inflammation in the body. It stopped the production of proteins that help mediate communication and reduced the production of chemicals that cause inflammation. Researched how energy stored in gelatin-covered PCL nanoparticles affects human mesenchymal stem cells [25]. The tiny NRG particles helped reduce swelling in cells. This means they can help protect the cells from harm when they don't get enough oxygen and glucose [18-20]. Their small medicine could be useful for treating stroke and other brain infections. Rajamani and others It was suggested to use a very small medicine mixture to keep the medicine strong and work well. They mixed things together using a method with a lot of pressure. In a bunch of tests, scientists looked at how well the tiny medicine worked to reduce inflammation compared to regular medicine and NRG. They did tests in the lab and on animals. The NRG with less in it helped swelling go down more than the normal NRG and diclofenac sodium [26].

An ischemic stroke can cause inflammation throughout the

body by allowing blood components into the brain. This occurs when the blood-brain barrier breaks down. In this instance, substances like NRG, which reduce swelling, appear to help prevent stroke and related health issues [24]. Ahmad and his team also conducted research on how NRG trapped in gelatin-coated PCL nanoparticles affects human mesenchymal stem cells. The decrease in inflammation signals suggests that NRG nanoparticles are effective in protecting the cells from damage caused by lack of oxygen and glucose. Therefore, their small medication may be beneficial for treating ischemic stroke and other brain diseases with inflammation (Figure 3) [25].

ANTIMICROBIAL ACTION

Right presently, individuals are curious about common items since they can murder germs and have less side impacts than man-made chemicals. These common items are secure and superior than anti-microbials since they are less likely to cause sedate resistance [27]. Microscopic organisms are not as likely to ended up safe to natural compounds since these compounds work in several ways to murder the microscopic organisms. Normal items can battle microbes by harming their external cover, ceasing their development, and anticipating them from staying together and communicating. NRG can murder numerous distinctive sorts of germs, like parasites and microscopic organisms. It works truly well against MRSA and extreme sorts of *H. pylori* NRG stops microscopic organisms from communicating with each other, which makes a difference it to battle off the microscopic organisms [28-30].

Current Issues Related with Naringin for Utilize in Healthcare

Naringin is used in the medical field, especially in cancer prevention and treatment. However, its effectiveness in patients has not been established due to poor absorption and breakdown in the body. When taken orally, only a small amount (about 8.8%) is retained, mainly due to breakdown by stomach bacteria. Naringin is not easily dissolved in water, making it difficult for the body to absorb it efficiently [25]. Studies have shown that naringin is most commonly studied when taken orally, but absorption in the stomach and body is slow and unpredictable. Intestinal bacteria play a positive role in influencing the effects of naringin and other flavonoids in the body [26]. There is a theory that altering the amount and potency of flavonoids, using small amounts to prevent breakdown by gut bacteria, could enhance their efficacy. However, implementing this theory in actual treatment is challenging. Intravenous administration of naringin also results in breakdown in the bloodstream and liver, primarily by a liver protein called "glucosidase." Research has indicated that naringin interacts with BSA in the body on an atomic level, affecting its metabolism, excretion, and utilization [27]. Major studies have focused on enhancing naringin delivery to the body using nanotechnology to prevent rapid elimination and adverse effects. These advanced delivery methods involve modifying specific targets to ensure slow and targeted drug release, ultimately improving naringin's effectiveness and reducing potential side effects. Therefore, combining naringin with a suitable nanocarrier can increase how much of it can be used by the body. The most recent nanosystems developed to improve the stability of NRG in recent years are being presented (Figure 4) [25-30].

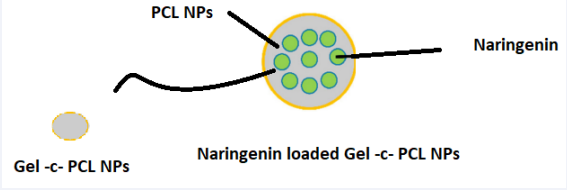

Figure 3 Using a specialized gelatin-coated material to assist human stem cells in dealing with a deficiency of oxygen and glucose more effectively.

CONCLUSIONS AND FUTURE DIRECTIONS

Some early ideas suggest that NRG could be used to treat many different illnesses because it has a wide range of effects on the body in both tests and animals. This natural product isn't used much in research before testing it on people because it doesn't dissolve well in water and can't be easily discussed. Nanotechnology is a great way to improve how we use energy and treat illnesses like cancer, inflammation, diabetes, and diseases in the liver, brain, and eyes. Scientists are testing it in the lab and on animals to make it work even better. Pure NRG can help treat infections, lung problems, and heart diseases when used with NRG-filled nanoparticles. Although NRG has only been tested in a few clinical trials, more research is needed to study the drug and how it affects people. Collecting information about how the human body interacts with these small details is important for understanding how they can be used in medicine and dietary supplements.

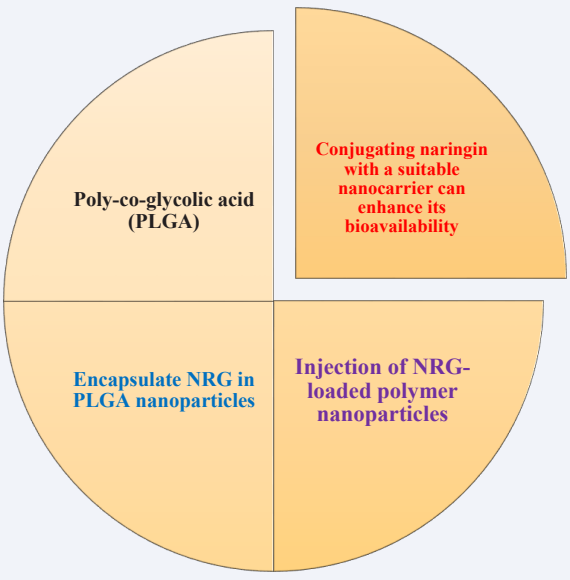

Figure 4 The most recent nanosystems have been developed to improve the stability of NRG.

Credit Authorship Contribution Statement

Mohammad Hossein Karami: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Majid Abdouss:** Supervision, Validation. **Behzad Aghabarari:** Supervision, Validation.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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