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Review Article

Nutraceuticals in Viral Infections: A Comprehensive Review on the Natural Occurrence and Therapeutic Potential of Resveratrol, Quercetin, and N-Acetyl Cysteine

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ABSTRACT

In recent years, there has been a growing interest in using nutraceutical supplements as adjuvants to treat viral infections. Nutraceuticals are food-derived, non-pharmaceutical substances that have demonstrated antiviral and other possible health advantages. The purpose of this review is to provide an overview of available data regarding the safety and efficacy of several nutraceutical supplements in the management of viral infections. Electronic databases and the reference lists of pertinent publications were used to perform a thorough search of the literature. The most widely used nutraceutical supplements for the treatment of viral infections were the subject of the search, which included both human and animal research. The review's findings imply that certain nutraceutical supplements, including N-acetyl cysteine, quercetin, and resveratrol, may be useful adjuvants in treatment of viral infections. The natural sources, modes of action, and therapeutic potential of these nutraceuticals in viral infections are highlighted in this review. Their effectiveness is supported by preclinical and clinical research, although more work is required to determine standardised dosage, bioavailability, and synergistic effects with traditional antiviral treatments. A viable method of treating viral infections may be provided by including these nutraceuticals into therapeutic and preventative plans.

Keywords: Nutraceutical, Antiviral treatments, Resveratrol, Quercetin, N-Acetyl Cysteine.

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INTRODUCTION

In recent years, dietary supplements that offer health benefits and serve as alternatives to modern medications have become more and more popular. Nutrients, herbs, and dietary supplements are the components that help preserve good health, combat various diseases, and improve quality of life.[1] Nutraceutical is derived from nutrition and pharmaceutical. DeFelice is credited with coining this term at the Foundation for Innovation in Medicine in 1989. In a news release in 1994, which reiterates and improves his definition. Nutraceutical is defined as "any substance considered a food or part of a food which provides medicinal or health benefits, including the prevention and treatment of disease." These encompass everything from processed foods like cereals, soups, beverages, herbal goods, and genetically engineered "designer" foods to diets, supplements, and isolated nutrients.[2] Natural or health-promoting substances that support the body are the ingredients in dietary supplements.[3] Dietary supplements are products derived from food sources that are said to provide additional health benefits beyond the basic nutritional value of food. In different jurisdictions, products may make claims to improve health, slow down ageing, prevent chronic illness, prolong life, or support body structure or function.[4] As a result of ongoing research efforts to ascertain the characteristics and potential uses of nutraceuticals, consumer demand and public interest in these goods have increased and continue to do so. The main factors propelling the growth of the functional food industry are current health and demographic trends. Globally, 4,444 people are ageing. While life expectancy continues to rise, the percentage of senior citizens in the general population is also rising. Furthermore, obesity is now recognised as a global concern due to its increasing prevalence in countries worldwide. In the United States, over 62% of the population is overweight [based on body mass index], and more than half of the 4,444 adults are classified as obese. Even in 4,444, where osteoporosis, arthritis and Cancer, heart disease continues to reign, heart disease continues to reign supreme, accounting for 32 % of all deaths [2.4 million per year] in the U.S. According to data from the International Obesity Task Force, the prevalence of obesity increased by 10-50% in most of European countries during the last ten years. Taking supplements and eating foods prepared

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or fortified with health-promoting components maximises the health-promoting potential of your diet. Another element influencing the expanding trend towards functional meals is public education. Nowadays, people are more worried about their food than ever before and are more interested in health-related knowledge found in a variety of educational resources.[5]

The shift towards nutraceuticals can be attributed to the following factors

1. The majority of therapeutic areas are covered by dietary supplements, such as blood pressure, cholesterol control, osteoporosis, depression, diabetes, sleep problems, colds and coughs, arthritis, digestion, and the prevention of some types of cancer.
2. They are using nutritional supplements to prevent chronic diseases and improve their health since they are fed up with using medications to do it.
3. Medical professionals should make sure that highly processed foods, which are frequently made from crops cultivated with genetically modified seeds, chemical fertilisers, pesticides, and herbicides do not contain the adequate amount required for optimum health. We are aware that it is devoid of nutrition.
4. The potential of nutraceuticals as therapeutic agents with curative and preventative qualities is quite promising.
5. People have chronic illnesses with which there are no effective symptomatic treatments.
6. Pharmaceuticals are quickly being replaced by dietary supplements in the prevention and treatment of both acute and chronic health issues.
7. Patients with limited resources and those who prioritise prevention over treatment.
8. More and more consumers are concerned about medical costs.[6,7]

Nutraceuticals for viral infections

A significant increase in infections induced by virus-associated mortality has led to an increased demand for safe and effective antiviral drugs. The development of drugs aimed at viruses is a challenge due to resistance paths, limited number of targets, rapid evolution of viral genes, and the introduction of new viral tribes through mutations. The WHO recorded around 22 different virus outbreaks in 2019 alone. Viral diseases such as Ebola virus [Democratic Republic of Congo and Uganda], Hantavirus [Panama and the Republic of Argentina], Zika virus [France], Middle East respiratory coronavirus [Merskov], Hantavirus [Revenue], Kingdom of Saudi Arabia, Oman, United Arab Emirates, Qatar]-measles [Madagascar, Europe, West Pacific region, Lebanon, Pacific countries and regions] and dengue fever [Jamaica, France, Pakistan, Sudan, Spain and Spain and Lipolisia Fghanistan], the virus outbreak is worsen every day. To formulate a framework for control, treatment, and mitigation of the risk of these viral outbreaks, independent of their source, WHO asserts that biorisk reduction dwells chiefly on the application of existing scientific knowledge concerning zoonoses, epidemic-prone orthopoxviruses, and viral hemorrhagic fevers. There are no specific drugs for each viral ailment, so the best methods are symptomatic therapy and immunological enhancement. Many innovative antiviral drugs have been developed in recent years; however, existing antiviral drugs still have inevitable disadvantages such as efficacy, toxicity, and price.[8] Various nutraceuticals with antiviral potentials and their mechanisms have already been discussed in the preceding sections.

Resveratrol

The polyphenolic stilbene compound resveratrol, also called 3,4',5-trihydroxy-trans-stilbene, is mostly present in fermented spermatophyte products. Figure 1 shows the chemical structure of resveratrol. This dietary supplement belongs to the known phytoalexin class and is usually produced in response to stresses such as pathogen attack or stress. Red wine grapes, peanuts, mulberries, etc. It contains a variety of antiviral properties and is useful in treating cardiovascular diseases and cancer. It can also increase longevity by scavenging superoxide, hydroxyls and lipid hydroperoxyl radicals. shown that potential is both *in vitro* and *in vivo* activity. Protects against arachidonic acid-induced mitochondrial dysfunction and reduces mitochondrial superoxide production. It also inhibits viral proteins, genes and nucleic acid synthesis at several levels.[9] Resveratrol exhibits antiviral activity against a wide range of viruses, including influenza, hepatitis C, respiratory syncytial, varicella-zoster, Epstein barr, herpes simplex, and HIV virus. Tests for African swine fever virus show favorable results. However, after RSV injection, the disease course was worsened in the case of HCV and Multiple Sclerosis [MS]. Resveratrol was added to the HCV replicon system OR6 *in vitro* in a dose-dependent manner, which markedly enhanced HCV RNA replication. In a similar vein, resveratrol treatment in mice with autoimmune Encephalomyelitis [EAE], a viral MS model, deteriorated the mice's health in comparison to controls.[10-12] A

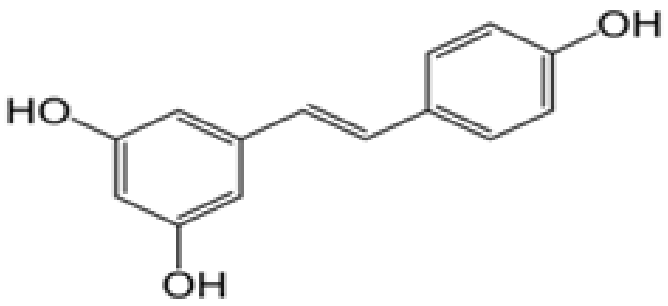

Figure 1: Structure of Resveratrol.

summary of resveratrol's presence in natural products is given in Table 1.

Quercetin

Quercetin is a member-specific chemical belonging to an important antioxidant nutrient group, bioflavonoids, also known by another name, flavanols, and is easily found in some tea, fruits, and vegetables. Figure 2 shows the chemical structure of Quercetin. Its effects are very rich, including antioxidant, antiviral, anti-inflammatory, antineoplastic, and signaling pathway modification. Since the quercetin works in a DNA way like the herpes viruses and in an RNA way like the coronaviruses and influenza, its antiviral effects are broad. The viral DNA replication and signaling pathways associated with post-transcriptional modulators are other areas of activity for post-viral healing through quercetin. Many studies have shown that cellular oxidative damage and the release of human metapneumonia virus and duck enteritis virus proinflammatory mediators and chemokines are suppressed when quercetin and resveratrol are given together.[23] Another study has shown that quercetin was able to effectively inhibit the entire replication cycle of the parainfluenza virus type 3 [Pf3] *in vitro* by blocking its DNA replication.[24] A summary of quercetin's presence in natural products is given in Table 2.

Table 1: Occurrence of Resveratrol in different natural products.

Sl. No.	Common name	Biological Source	Parts	Quantity	References
1	Grapes	*Vitis vinifera*	-	1 to 10 mg/kg	[13]
			grape skin	5-10 mg/kg	[14]
			Grape [Black]	0.15 mg/100 g FW	[15]
			Grape [Green]	0.02 mg/100 g FW	[15]
			Grape [Green], pure juice	5.08e-03 mg/100 mL	[16]
			Red wine	0 - 2780 µg/100 mL	[17]
			Rose wine	5-290 µg/100 mL	[17]
			White wine	0-170 µg/100 mL	[17]
			Sparkling wine	8-10 µg/100 mL	[17]
2	Japanese knotwood	*Polygonum cuspidatum*	-	2.96 to 3.77 mg g^{-1} dry weight	[18]
			Perennial roots	1024.96 μg^{-1}g dry weight	[19]
			Leaf	764.74 μg^{-1}g dry weight	[19]
			Stem	123.57 μg^{-1}g dry weight	[19]
			Annual roots	26.88 μg^{-1}g dry weight	[19]
3	Berries				
	Bilberry	*Vaccinium myrtillus*	Fruit	6.78 µg/g of FW	[20]
	Cowberry	*Vaccinium vitis-idaea*	Fruit	30 µg/g of FW	[20]
	Cranberry	*Vaccinium oxycoccus*	Fruit	19.29 µg/g of FW	[20]
	Strawberry	*Fragaria ananassa*	Fruit	3.57 µg/g of FW	[20]
	Red currant	*Ribes rubrum*	Fruit	16.66 µg/g of FW	[20]
	Mulberries	Morus	Skin	50 µg/g dry weight	[21]
4	Cocoa powder	*Theobroma cacao*	Powder of seeds or beans	0.28 - 0.46 mg in 200 g	[21]
5	Peanuts	*Arachis hypogaea*	Peanuts [raw]	0.01-0.26 mg in 146 g	[22]
			Peanuts [boiled]	0.32-1.28 in 180 g	[22]
			Peanut butter	0.04-0.13 in 258 g	[22]

Table 2: Occurrence of Quercetin in different natural products.

Sl. No.	Common name	Biological Source	Parts	Quantity	References
1	Caper	*Capparis spinosa*	Canned	172.55 mg/100 g	[25]
			Raw	233.84 mg/100 g	
2	Dill weed	*Anethum graveolens*	Fresh	55.15 mg/100 g	
3	Oregano	*Origanum vulgare*	Fresh	7.30 mg/100 g	
			Dried [Mexican]	42.00 mg/100 g	
4	Tarragon	*Artemisia dracunculus*	Fresh	10.00 mg/100 g	
5	Acerola	*Malpighia emarginata*	Raw	4.74 mg/100 g	
6	Coriander	*Coriandrum sativum*	Leaves, Raw	52.90 mg/100 g	
7	Fennel	*Foeniculum vulgare*	Leaves, Raw	48.80 mg/100 g	
8	Lovage	*Levisticum officinale*	Leaves, Raw	170.00 mg/100 g	
9	Onions	*Allium cepa*	Raw	21.40 mg/100 g	

Table 3: Occurrence of N-Acetylcysteine in different natural products.

Sl. No.	Common name	Biological Source	Parts	Quantity	References
1	Onion	*Allium cepa*	Whole	45 mg/kg	[27]
2	Asparagus	*Asparagus officinalis*	Whole plant	46 nM/g wet Weight	[28]
3	Cucumber	*Cucumis sativus*	Whole plant	6 nM/g wet Weight	
4	Parsley	*Petroselinum crispum*	Whole plant	9 nM/g wet Weight	
5	Tomato	*Solanum lycopersicum*	Whole plant	3 nM/g wet Weight	
6	red pepper	*Capsicum annuum*	Whole plant	25 nM/g wet Weight	
7	green pepper	*Capsicum annuum*	Whole plant	12 nM/g wet Weight	
8	Lemon	*Citrus limon*	Fruit	4 nM/g wet Weight	
9	Grapefruit	*Citrus paradisi*	Fruit	4 nM/g wet Weight	
10	Strawberry	*Fragaria ananassa*	Fruit	5 nM/g wet Weight	

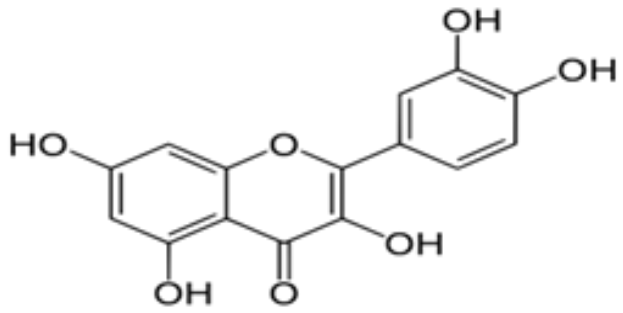

Figure 2: Structure of Quercetin.

N-Acetyl Cysteine

The main uses of the prodrug N-acetylcysteine are as a mucolytic and to treat acetaminophen intoxication. Figure 3 shows the chemical structure of N-acetyl cysteine. This compound's antiviral action is significantly influenced by its anti-inflammatory and antioxidant qualities. Nevertheless, the molecular mechanism of action of NAC's antiviral effect is still mostly unclear. It does, however, inhibit viruses that cause human disease with totally different etiologies from SARS-CoV-2, such as HIV and other viruses with similar replication mechanisms [dependence on nuclear transcription factors for infectivity]. The lower oxygen levels present in a host cell also contribute to viral pathogenesis, with reduced or no GSH available in addition to general biological stress factors which are also associated with this upregulation of free radicals and inflammatory signaling molecules. It's true. Similar to prodrugs that boost GSH to aid the body's defence against certain viruses.[26]

A typical supplement and medication is N-acetylcysteine [NAC], which is derived from the amino acid cysteine. Although NAC is not widely distributed in nature, it is present in trace amounts in several vegetables and natural goods. Demirkol *et al.* [2004] used High-Performance Liquid Chromatography [HPLC] to examine the amounts of biological thiols, including NAC, in various vegetables and natural goods.

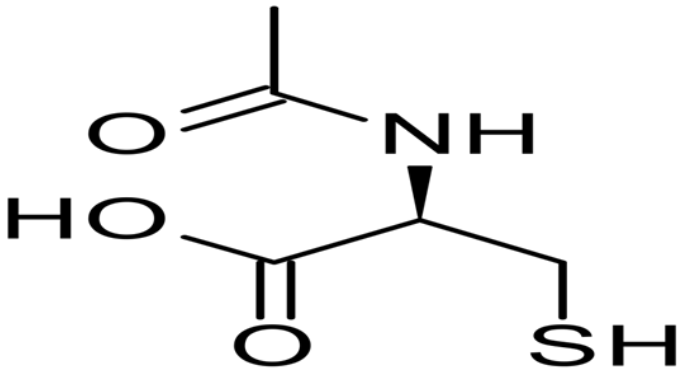

Figure 3: Structure of N-Acetyl Cysteine.

It's crucial to remember that a variety of factors, including the plant's growth conditions, maturity, and post-harvest management, might affect the presence and concentration of NAC. Additionally, the study discovered that cabbages, red grapes, blackberries, apples, and peaches did not contain any of the biological thiols examined, with the exception of NAC.

These results demonstrate that although NAC is found in several natural goods and vegetables, its levels are very modest and vary among different plant species. A summary of N-Acetylcysteine's presence in natural products is given in Table 3.

CONCLUSION

There is promise in using nutraceuticals to treat and prevent viral infections. Because they frequently have fewer side effects and can be more affordable, they are a promising adjunct to or substitute for conventional pharmacological treatments. It is crucial to remember that more investigation is required to completely comprehend the mechanisms of action and ideal dosages for these drugs. Before adding nutraceuticals to your treatment plan, it's crucial to speak with a healthcare provider because they might interfere with other medications or be contraindicated for specific people. All things considered, nutraceuticals present a promising strategy for managing and preventing viral infections, and more research is necessary to fully understand their potential.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ABBREVIATIONS

U.S: United States; **WHO:** World Health Organization; **DNA:** Deoxyribonucleic Acid; **RNA:** Ribonucleic Acid; **NAC:** N-Acetyl Cysteine; **HIV:** Human Immunodeficiency Virus; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2.

AUTHOR CONTRIBUTIONS

Sanket R. Vakte designed the framework for the review and conceptualized the study. also performed the literature search, reviewed relevant articles, and wrote the manuscript. Jitendra Y. Nehete helped analyse the therapeutic Potential of nutraceuticals and facilitated the selection of appropriate data and content for inclusion. Chinmay P. Sonawane and Vaibhav K. Pawar reviewed and edited the manuscript critically for accuracy, and clarity. Authors have all read and approved the manuscript's final version.

ETHICAL APPROVAL

The authors conduct their research and gather data from secondary sources in accordance with ethical standards. Every reference was properly cited and acknowledged.

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