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A Comprehensive Review On Quercetin Nano-Formulations For Topical Applications

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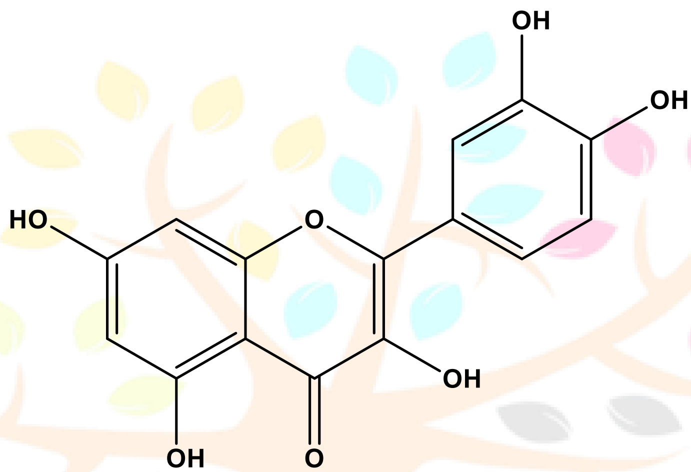
ABSTRACT: Since ancient times, atopic dermatitis (AD) has been recognized as a frequent skin condition. QUR exhibits anti-obesity, anti-diabetic, anti-allergic, anti-neoplastic, neuroprotective, antibacterial, and antioxidant actions, which are indicative of its potential therapeutic characteristics. Furthermore, because QUR has a lo bioavailability, several techniques to improving its bioavailability and delivering novel therapeutic approaches have been developed, including QUR loaded mucoadhesive nanoemulsions, QUR polymeric micelle, QUR nanoparticles, glucan-QUR conjugate, and QUR loaded gel. Quercetin is well-known for its anti-allergic and antioxidant qualities, which include scavenging free radicals, boosting immunity, preventing the release of histamine, lowering the production of leukotrienes, inhibiting the production of interleukin (IL-4), and decreasing pro-inflammatory cytokine levels. It can suppress the production of IgE antibodies specific to antigens and balance the Th1/Th2 ratio. It is also useful in suppressing inflammatory mediators and inhibiting enzymes including lipoxygenase, eosinophil, and peroxidase.

INDEX TERMS: Quercetin; atopic dermatitis, QUR loaded gel, antiallergic properties.

INTRODUCTION:

Quercetin is a yellow substance that is crystalline and has a bitter taste. It is insoluble in water and is classified as an aglucone or aglycon since it eliminates carbohydrates from its structure. It gives blooms of different hues [1]. One of the major elements of the human diet is quercetin, a secondary metabolite that exists in a number of plants [2].Depending on the cultivars or development circumstances, plant foods contain different quercetin contents [3-5]. One of the main bioflavonoids, quercetin acts as the foundation for many more flavonoids [6].

There are several flavonoids that have therapeutic value, including quercetin . Onions, apples ,broccoli, tea and redwine are also abundant in it. Its rapid clearance, rapid metabolism, and enzymatic breakdown restrict its potential to therapeutic affect despite its wide range of therapeutic applications. To get over these problems, several types of medication delivery methods have been studied [7]. Dietary flavonoids, which or QUR (3, 5, 7, 3′, 4′-pentahydroxyflavone), frequently occur in blossoms, leaves, alcohol, coffee and tea, veggies, bark roots, as well as other plant-based compounds. Chemically speaking, these are made up of 3 rings of benzene and five hydroxyl groups. Oxygen-containing heterocyclic ring C, both aromatic rings A and B, and hydroxyl groups are shown (figure-1)



Chemical Formula: $C_{15}H_{10}O_7$

Exact Mass: 302.0427

Flavonoids such as quercetin are widely used in medicine for their therapeutic properties. Its rapid clearance, fast metabolism, and enzyme breakdown reduce its potential for therapeutic impact, despite its wide range of therapeutic applications. To get around these problems, several types of medication delivery methods have been tested[8].

Quercetin is an IUPAC name for 3, 5, 7, 3', 4'-pentahydroxy flavones, a member of the flavonoid family. It comprises of 3 rings, 5 hydroxyl groups, and two aromatic rings, A and B, linked by a heterocyclic ring C containing oxygen. The B ring includes a number of hydroxyl groups in parallel to another methoxy group.Polyphenols are chemical substances found naturally in plants. Generally speaking, polyphenols fall into two major categories, each comprising roughly 8,000 compounds: There are other instances of both 1avonoids and non-1avonoids, such as phenolic acids, lignans, stilbenes, and other polyphenols[9]. Quercetin is synthesized by plants in a variety of glycosidic forms. It usually occurs in conjugated forms with galactose, glucose, and rhamnose [10]. The richest resources for quercetin. It is made up of five hydroxyl groups and three benzene rings chemically.

Quercetin has three key properties: antioxidant, anti-inflammatory, and immunomodulatory. Quercetin may be beneficial for any adverse illness involving inflammation, oxidative stress, or immunity due to its combined properties. These conditions include a broad spectrum of disorders that may be linked to the health of the bones and joints, the respiratory system, the stomach, the cardiovascular system, and the process of healthy aging. [11]Several therapeutic plants, including Hypericum species, American elderberries, and gingko, have been reported to contain quercetin [12].

1. Physiochemical Properties Of Quercetin

At 313–314 °C, quercetin melts into a needle-shaped yellow crystal. The chemical formula C15H10O7, and the molecular mass is 302.23. Quercetin is also goes by the names 3,3′,4′,5,7-pentahydroxyflavone and 3,3′,4′,5,7-pentahydroxy-2-phenylchromen-4-one. In the class flavonoids, quercetin belongs to the subclass called flavonal. It is made up of a three-carbon pyrone ring (C) connecting two aromatic rings (A and B). It is soluble in ethanol, methanol, as well as in ethyl acetate; slightly soluble in petroleum ether, benzene, ether, and chloroform; and less soluble in water [13].

2. Pharmacokinetic Activity Of Quercetin

In addition to its weak permeability, low bioavailability, poor solubility, and instability, QC has limited applicability in the pharmaceutical industry. Many strategies, encasing the use of potential drug delivery methods such as inclusion complex, liposomes, nanoparticles, micelles which offer better solubility and bioavailability have been tried to improve the bioavailability of QC [14].

3. Pharmacological Activity

3.1 Anticancer

In addition to being a low-toxicity medicinal molecule for the treatment of cancer, quercetin can be utilized as a supplement to prevent cancer [15].Though their efficacy and selectivity remain restricted, bioflavonoids have recently drawn significant attention as a novel class of chemotherapeutic drugs against various kinds of malignant tumors. [16]When biologists refer to oxygen radicals, superoxide, hydroxyl, peroxyl, and alkoxyl, as well as other nonradicals that are oxidizing agents, they are all collectively referred to as ROS. [17]

3.2 Anti-Inflammatory

It has been established that quercetin, a component of flavonoids, has long-acting anti-inflammatory properties [18,19].Quercetin has been demonstrated time and time again to exhibit anti-inflammatory effects on /macrophage system in vitro, in addition to a broad spectrum of biochemical and pharmacological actions [20,21]. Because of their different properties(anti-inflammatory,antipyretic and analgesic), non-steroidal antiinflammatory medicines (NSAIDs) are frequently utilized. There is a high risk of toxicity with both acute and long-term usage of several NSAIDs. A variety of compounds with interesting biological and pharmacological properties can be found in medicinal plants [22].

3.3 Cardiovascular Protection

Due in large part to quercetin's anti-inflammatory and antioxidant characteristics, it has a positive impact on cardiovascular illnesses such as hypertension, atherosclerosis, ischemia-reperfusion injury, and cardiotoxicity [23,24]. According to research, quercetin, a flavonoid found in Ugni molinae Turcz. (murtilla) fruits, has the ability to dilate blood vessels and perhaps lower blood pressure through the activation of calcium-dependent potassium channels [25]. Quercetin is noteworthy because it has the ability to selectively activate vasorelaxant KCa1.1 channels while simultaneously inhibiting the activity of Ca channels, potentially decreasing blood pressure [26].Quercetin use may help lower the risk of cardiovascular disease (CVD). [27]

3.4 Antioxidant Activity Of Quercetin

As a safe dietary polyphenol, quercetin can be used to prevent lipid oxidation [28].Due to its high-quality antioxidant activity, quercetin is one of the phenolic substances that is most frequently examined. Because of its flavonoid structure a 2,3 double bond combination with a 4-oxo bond in quercetin's C ring. It shows wide resonance and permits delocalization of electrons from the B ring. As a result, radical scavenging has high efficiency [29]. Hence, quercetin's structure is more effective at promoting antioxidant activity than anthocyanins' structure.Quercetin has strong antioxidant properties based on its polyphenol structure; when combined with free radical species, it produces phenoxy radicals that are noticeably less reactive [30].

Additionally, quercetin's antioxidant properties lessen the cell death that oxidative stress causes in keratinocytes [31] Like myricetin, fisetin, and catechin, quercetin is a powerful inhibitor of lipid oxidation and belongs to the class of flavonoid aglycones with 3-OH groups [32].Quercetin stops the chain from propagating by inhibiting the chain oxidation start phase. This can also involve a chain breaking dueto a two-radical reaction [33,34]. Quercetin, however, prevented radiation causing brain damage , acrylamide-inducing oxidative stress, radiation causing brain damage in rats, and nerves damage in the retinas of diabetic rats in a variety of experiments. These experiments were carried out in response to cadmium fluoride and its related neurodegenerative disorders [35, 36].

3.5 Antimicrobial Activity

Antibacterial properties of quercetin have also been demonstrated against several kinds of Gram-positive bacteria, such as Standard Enterococcus, Methicillin-sensitive S. aureus (MSSA), and Methicillin-resistant Staphylococcus aureus (MMRSA).[37] It is essential to remember that myricetin, quercitin, chrysin and kaempferol are the flavonols that are most prevalent in food. Research examined the antimicrobial and anti-inflammatory properties of quercitin, chrysin, and kaempferol. [38] Flavonoids exhibit direct antibacterial activity when bacterial cells are exposed to polyphenols, and they can also exhibit indirect antibacterial activity by influencing the virulence characteristics of pathogens.

3.6 Antiviral Activity

Many types of viruses have been demonstrated to be immune to quercetin's antiviral action. For example, quercetin has been found to be effective against the human T-lymphotropic virus 1 and the Japanese encephalitis virus (JEV), which is responsible for the mosquito- borne disease known as Japanese encephalitis.[39] In another study, quercetin was demonstrated to have a more targeted method of action, decreasing dengue virus type-2 reproduction but not the attachment or entry processes of the virus [40].

4. ATOPIC DERMATITIS (AD)

Atopic dermatitis (AD), often known as eczema is a recurrent, chronic, and frequently extremely itchy inflammatory skin condition. According to a recent epidemiology study that used national data, most of the United States[41] may have a pediatric prevalence of at least 10%. The public's attention has recently been drawn to allergic disorders because of the rising prevalence of these conditions in general and AD in particular.Skin irritation with multiple morphologies is called dermatitis.Itching, blistering, swelling, and redness are the hallmarks of the acute phase. As the wound heals, crusts and scales emerge. The symptoms of the chronic phase include fissures, hyperkeratosis, and dryness. Atopic dermatitis and contact hypersensitivity are the two most common types of dermatitis [42].

AD has long been thought to be mainly a childhood illness; mostly in children varies from 2.7% to 20.1% across different countries and from 2.1% to 4.9% in adults.[43] Its clinical presentation and mode of onset also have different phenotypes, ranging from persistent form in childhood to late- onset forms in adulthood or in the elderly[44].The last ten years of the 20th century have seen the emergence of novel therapeutic techniques [45,46] as well as new approaches that may be crucial for our comprehension of the disease. [47,48] .A recent review has examined the numerous genetic studies on AD that have been published [49].

4.1 Quercetin-loaded nanoparticles for topical delivery

The human skin is the biggest organ in the constantly in contact with the environment. Topical antioxidant quercetin has been shown to delay UV radiation-induced oxidant damage and cellular death through the scavenging of oxygen radicals, protecting lipids from peroxidation to stop the chain-radical reaction, and chelating metal ions to create inert complexes that stop superoxide and hydrogen peroxide from converting into hydroxyl radicals.[50] According to their nanoscale size, they have a number of benefits in comparison to the commonly utilized solid and liquid dosage dosage forms, including tablets, capsules, suspension and emulsion. These stem from their physicochemical characteristics, particularly their composition of components (lipids, surfactants, amphiphilic block copolymers, etc.) and size [51].

4.2 QUR loaded gel

The most soluble in cinnamon oil was prepared NE, including QUR, followed by triacetin, castor oil, sesame oil, labrafac, palm oil, and isopropyl myristate; the least soluble in the oil was miglitol. The results of the research indicated that the physical characteristics, stability, sol-gel transition, and injectability of the gel were improved by mixing QUR with cinnamon oil, tween 80, carbitol®, and poloxamer 407. When this formulation was administered to patients with periodontitis, in vitro experiments on the patients' conditions showed encouraging improvements [52].

4.3 Hydrogels

The best hydrogel was QUE hydrogel; it had a sodium alginate:PVA ratio of 2:1. This hydrogel showed the best viscosity behavior, the fastest rate of swelling, and the best penetration in ex vivo skin models [53].A hydrogel with high wound-closing effectiveness was made of platelet-rich plasma and SA [54]. The hydrogel was prepared by a straightforward, one-step thrombin activation procedure. The results of the morphological characterization showed the hydrogel's three-dimensional network structure. Then, in hydrogel produced in phosphate buffer solution (PBS), specific concentrations of VEGF and EGF were found, suggesting the potential for vascular regeneration and cell proliferation. The hydrogel showed good wound closure efficacy when applied topically to rats' injured skin [55]. Hydrogel scaffolds, one of the many 3D scaffolds used in tissue engineering, have attracted particular attention because of their distinctive qualities, which include moisture retention, porosity, natural extracellular matrix (ECM) mimicking, biocompatibility, biodegradability, and biocompatibility [56].

4.4 Quercetin-Containing Liposomes-Gel

Liposomes embedded within a gel matrix for medication delivery exhibit a delayed release of the drug [57] and enhanced bioavailability. This is facilitated by the three-dimensional network structure of the hydrogel, which improves adherence to the skin surface, particularly beneficial for dermal eczema treatment.More skin permeability was shown by quercetin than by rutin. Additionally, we discovered that, in comparison to single systems of hydrogel (quercetin, 31.77%; rutin, 26.35%), liposome (quercetin, 48.35%; rutin, 37.41%), or control (phosphate buffer,pH 7.4), liposome-in-hydrogel complex systems (quercetin, 67.42%; rutin, 59.82%) improved the skin permeability of quercetin and rutin. [58]. This study was designed to create quercetin-containing liposomes-in-gel (QU-LG), assess its antioxidant properties, and test its potential as a preventive and therapeutic agent for cutaneous eczema by applying it to dermal eczema-affected mice's skin [59].

CONCLUSION:

QUR is a phytochemical that has been shown to protect against several illnesses. Some research, however, demonstrated that the human body does not absorb it well. Novel approaches that improve QUR bioactivity in people, reduce expenses, and are more easily explained during clinical exams have recently been put presented. Additionally, new extraction techniques were developed by researchers to improve the extraction yield of QUR. Future research can also concentrate on reducing the drawbacks of the previously stated techniques, and integrating one or more extraction techniques can also be an alternative to enhance the outcomes. A few non-invasive techniques have also been developed recently for assessing QUR in agricultural goods. These techniques are quick, safe for the environment, non-destructive, and allow for online detection. However, these approaches' shortcomings can be improved upon to increase their applicability in more research fields. Its applications can be expanded through the development of new chemometric models, techniques to address auto-fluorescence problems in fluorescence spectroscopy, solutions to the scattering phenomenon in terahertz spectroscopy, and advancements in near-infrared spectroscopy's capacity to identify volatile compounds in food. Additionally, surface-enhanced Raman spectroscopy can be made more sensitive and dependable as a sensing platform by using robust, repeatable, sensitive nanoparticles and algorithms for quick processing of raw data and data mining techniques. Additionally, combining these non-invasive techniques can result in an analytical instrument that is quicker, more sensitive, and more accurate ssfor identifying phytochemicals in a variety of fruits and vegetables.

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