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Unveilling Flavonols: Structures, Properties and Synthesis

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Abstract

Flavonols are a major subclass of flavonoids that are widely distributed in the plant kingdom and essential to the human diet. This work explores their fundamental characteristics, ranging from their chemical structure based on the 2-phenylchromen-4-one system to their abundant natural sources such as onions, grapes, and tea. The study details the physicochemical properties of flavonols as well as advances in their extraction methods, including the use of natural deep eutectic solvents (NaDES) as a sustainable alternative. Finally, the article highlights the importance of their biological activities, particularly their antioxidant power, and the diversity of their fields of application, from agriculture to medicine. Scopus indicates that more than 21430 articles were published from 1904 to 2025. China and the US are the wide Countries contributing.

Keywords: Flavonols; Flavonoids; Chemical Structure; NaDES; Antioxidant activity; Bibliometric analysis.

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1. Introduction

This article reviews the main sources of flavones and their concentrations in foods and beverages, which vary considerably from one study to another. Flavones are a class of flavonoids that are attracting growing interest due to their biological activities in vitro and in vivo. Flavonoids are polyphenolic phytochemicals found in fruits, nuts, and vegetables. Dietary intake of these structurally diverse compounds is associated with numerous health benefits, including increased life expectancy, a reduced risk of cardiovascular disease, and a lower incidence of metabolic disorders (Martinez *et al.*, 2019; Safe *et al.*, 2021; Merimi *et al.*, 2025; Kadda *et al.*, 2026). Flavonoids are a widely distributed group of natural polyphenolic compounds found in plants (Diass *et al.*, 2021; Bitari *et al.*, 2023 and 2024; El Guerrouj *et al.*, 2023; Haddou *et al.*, 2024), usually in glycosylated form, and have been shown to possess a wide range of biological activities, including antioxidant, anti-inflammatory, antibacterial, antiviral, and antiallergic properties, making them an interesting target for synthesis and further study (Ghedira, 2005). Among flavonoids, flavones and flavonols are related in that they have the same basic skeleton, the 2-phenyl-chromen-4one system. Flavonols are one of the most studied subclasses of flavonoids due to their wide distribution in plants and their great structural diversity (Ghedira, 2005). Flavonols are plant pigments found in vegetables, plants, and crops such as onions, apples, green tea, and grapes. They are therefore widely present in our diet and have positive effects on human health. We will therefore study some of their properties, such as their physicochemical properties, their derivatives, and their method of synthesis. Bibliometric analysis, or bibliometrics, has been used for several decades to evaluate scientific research. It uses bibliographic data to measure and study various aspects of a specific field of scientific activity, including the evaluation and analysis of the productivity and impact of researchers and technologies, the identification of trends in scientific research, the reconstruction of the history of a scientific field's development, and the identification of research topics (Tang & Walsh, 2009; Salim *et al.,* 2022; Elmsellem, *et al.*, 2023; Laita, *et al.*, 2024; Hammouti, *et al.*, 2025; Merzouki, *et al.*, 2025; Salghi, 2025). The high increase of articles from 6 articles to over 1400 articles in 2025, among the 21433 Scopus documents, reflects the wide concern of researchers and police makers in natural plants and especially in flavonols (**Figure 1**).

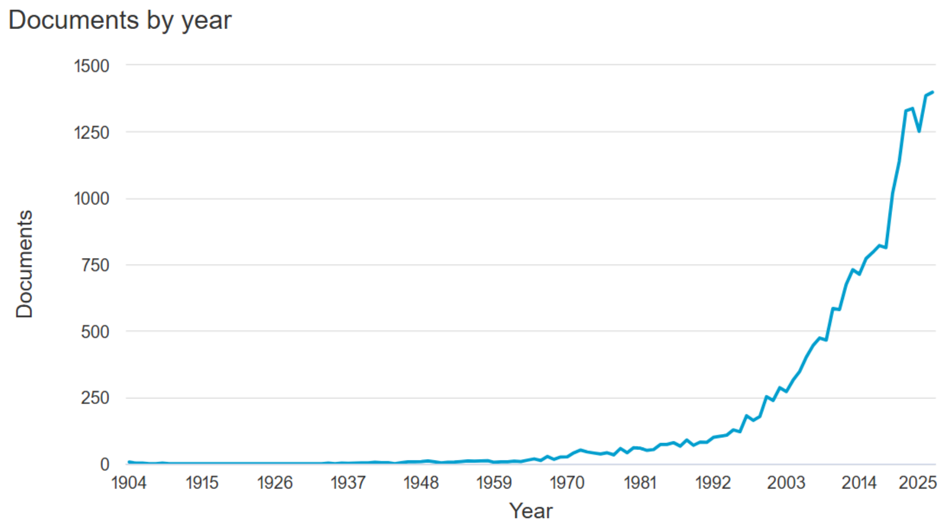

Figure 1: Evolution on flavonols articles from Scopus-Elsevier (1904-2025)

Figure 2 shows the ranking of the top ten countries in terms of scientific publications (documents) in the field of study. An analysis of the data reveals a marked dominance of China, which ranks first with approximately 4757 documents, followed by the United States with approximately 2400 publications.

Spain ranks third worldwide and first in Europe, with more than 1417 documents. The rest of the ranking is mainly occupied by European nations such as Italy, and Germany, whose output ranges from 1405 to 1305 documents. Finally, India, fifth position reaches the 1400-document threshold. This geographical distribution highlights an intense international research effort, with a major concentration of research work in North America, East Asia, and Europe.

Figure 3 shows the most productive authors in the field of flavonols, ranked by number of publications. Iwashina, T. ranks first with the highest number of documents (approximately 83 publications), followed by Harbone, J.B. and Wollenweber, E., who also have a significant scientific output (83 and 72 articles, respectively). Other authors, such as Veneric, R., Wojdilo, A., and Mabry, T.J., have an intermediate number of publications. This distribution highlights a concentration of scientific output around a small group of researchers heavily involved in the study of flavonols, reflecting their major role in advancing knowledge in this field.

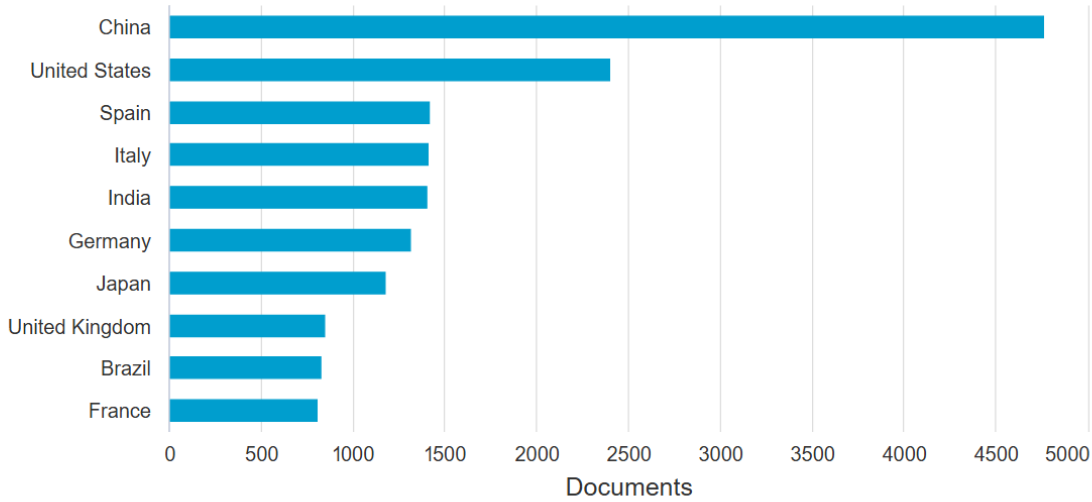

Figure 2: Top countries working on flavonols from Scopus-Elsevier (1904-2025

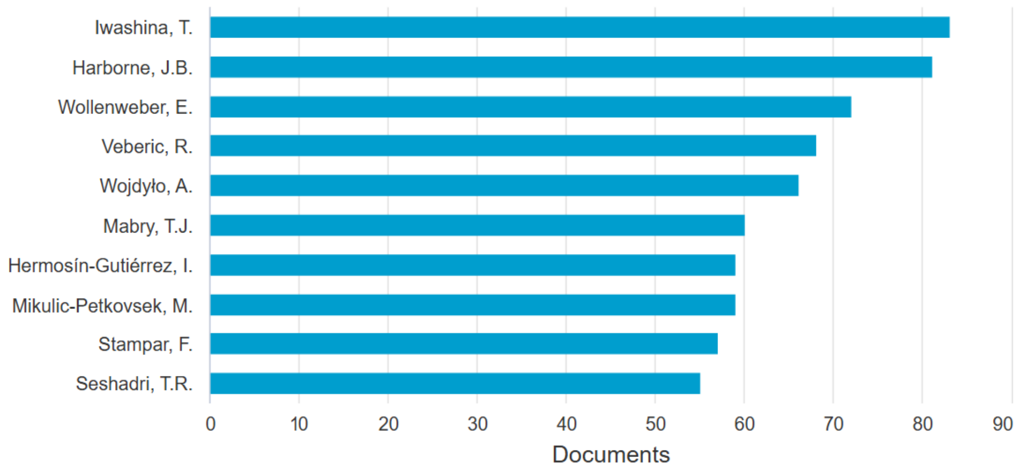

Figure 3: Top authors working on flavonols from Scopus Elsevier.

2. The history and sources of flavonols

2.1. History of flavonols

Flavonoids were discovered by Albert Szent-Györgyi of Nagyrápolt (September 16, 1893 in Budapest – October 22, 1986 in Woods Hole, Massachusetts) his photo below. This eminent scientist was awarded the Nobel Prize in Physiology or Medicine in 1937, primarily for his work on vitamin C. At the time of their discovery, flavonoids were initially referred to as "vitamin P" (Grzybowski and Pietrzak, 2013).

Albert Szent-Györgyi de Nagyrápolt

2.2 **Sources of flavonols:** Flavonols are one of the most common subgroups of flavonoids in our diet. They are found in abundance in a wide variety of vegetables such as red onions, spinach, broccoli, kale, cherry tomatoes, and celery. In terms of fruit, they are particularly present in apples, apricots, grapes, olives, plums, blueberries, cranberries, elderberries, currants, and blueberries (**Figure 4**). They are also found in cereals such as buckwheat and beans (green/yellow). Finally, significant concentrations are found in other sources, including red wine, tea (green, black), cocoa powder, turnips (green), leeks, endives, tea (black drink), and spices and herbs such as dill. (Hollman, *et al*., 1997; McAnlis, *et al*., 1999).

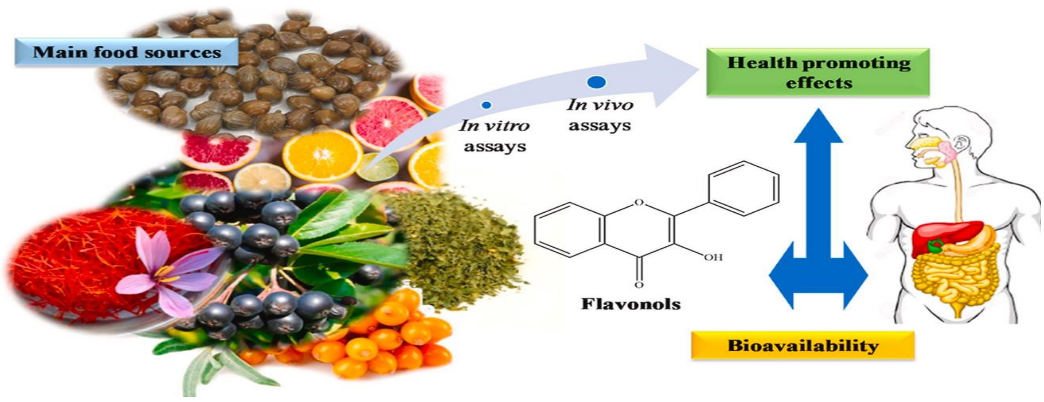

Figure 4: Sources of flavonols. (Barreca, *et al*., 2021)

Fruits, vegetables, and beverages such as tea and red wine are particularly rich sources of flavonols. (Crozier, *et al*., 1997; Hertog, *et al*., 1993) Tea, onions, and apples are the main dietary sources of flavonols in the Netherlands (Hertog, *et al*., 1993), Denmark (Justesen, *et al*., 1997), and the United

States (Rimm, *et al.*, 1996). However, dietary sources can vary significantly depending on the country of origin. (Hertog, *et al.*, 1995) These differences are influenced by dietary habits and cultural changes.

3. The chemical structure, derivatives, and properties of flavonols

3.1. Chemical structure: Flavonol or 3-hydroxyflavone (3-hydroxy-2-phenylchromen-4-one in IUPAC nomenclature) refers to flavonoids with a phenolic hydroxyl group at C3 and a carbonyl group C=O at C4 on the central heterocycle of the flavonoid base skeleton (**Figure 5**).

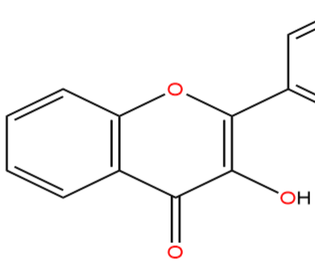

Figure 5: The chemical structure of flavonol (Ghedira, 2005)

3.2. Flavonol derivatives: Commonly, flavonols contain a central structure of 3-hydroxyflavones, also known as (3-hydroxy-2-phenylchromen-4-one), and are widely found in dietary fruits, green vegetables, beverages, and certain medicinal plants and herbs (Spagnuolo, *et al.*, 2018) Not all of the derivatives are flavonols, as pachypodol is not a definite flavonol but can be transformed from its hydroxyl group to a methoxy group, which shows a structural appearance of 3-hydroxyflavone, a flavonol. Flavonols are found in various forms, such as (shown in **Figure 6**).

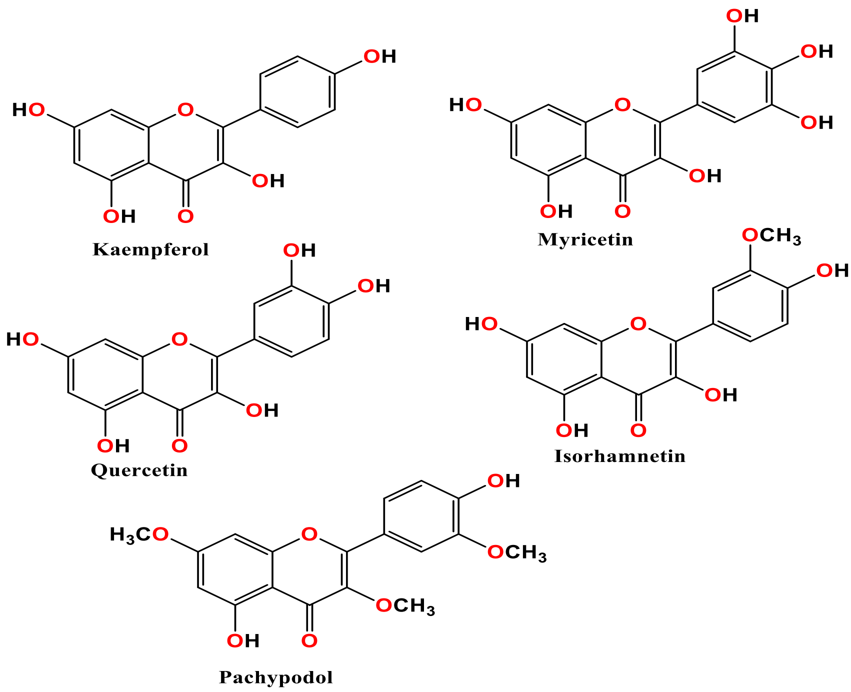

Figure 6: Examples of some flavonol derivatives

3.3. Physicochemical properties: Flavonol, a compound belonging to the flavonoid family, has the chemical formula $C_{15}H_{10}O_3$. Its molar mass is 238.24 g/mol, which allows the quantities required for synthesis or analysis reactions to be determined precisely. It has a melting point between 171°C and 172 °C, and flavonol is also soluble in ethanol, making it compatible with many organic solvents used in laboratories (National Center for Biotechnology Information (NCBI, 2024).

4. Method of extraction and synthesis of flavonols

4.1. Ultrasound-assisted extraction (UAE): In the literature, most studies on the extraction of flavonols from onions have used solvents such as methanol (Bonaccorsi, *et al.*, 2008; Ko, *et al.*, 2018), even though it is toxic to the environment and poses risks to researchers. Recent studies have therefore proposed the use of NaDES as a sustainable alternative for extracting flavonols from onion matrix.

4.2. Extraction solvent: Deep eutectic solvents (DES) are considered an interesting alternative to conventional solvents (**Figure 7**). They consist of a mixture of two or more components, usually a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD) (Huang, *et al.*, 2025). These components interact with each other through hydrogen bonds, forming a mixture with a lower melting point than each of the components taken separately (Khalid, *et al.*, 2025; Lianza and Antognoni, 2024). When these eutectic mixtures are prepared from abundant natural molecules, they are called Natural Deep Eutectic Solvents (NaDES). NaDES are generally composed of natural substances such as choline, sugars, organic acids, amino acids, and natural alcohols (Pani, *et al.*, 2019). From a green chemistry perspective, (NaDES) offer several advantages, including low volatility, good biodegradability, and stability at room temperature (Gomez-Urios, *et al.*, 2022).

4.3. Extraction method: Flavonols were extracted using an Elmasonic S15H ultrasonic bath (Elma Schmidbauer GmbH, Germany) operating at a frequency of 37 kHz and a maximum power of 280 W. For each test, a sample of freeze-dried onion (between 0.05 and 0.2 g) was placed in a 10 mL Falcon tube and mixed with 5 mL of extraction solvent (The mixture of choline chloride/levulinic acid (1:2) proved to be the most effective for extracting the main flavonols from onions), thus adjusting the solid-liquid ratio according to the experimental conditions. The mixture was then subjected to ultrasonic treatment at a controlled temperature and duration, using a Lauda (France) cooler to ensure the thermal stability of the medium (González-de-Peredo, *et al.*, 2025). Once the compounds of interest had been extracted, the supernatant was separated from the solid onion residue by centrifuging the sample at 1164 x g for 15 min. A volume of 2.5 mL of this supernatant was transferred to a 5 mL volumetric flask, which was then filled to the mark with water. The final extracts obtained were stored in the freezer until their subsequent analysis by LCMS/MS.

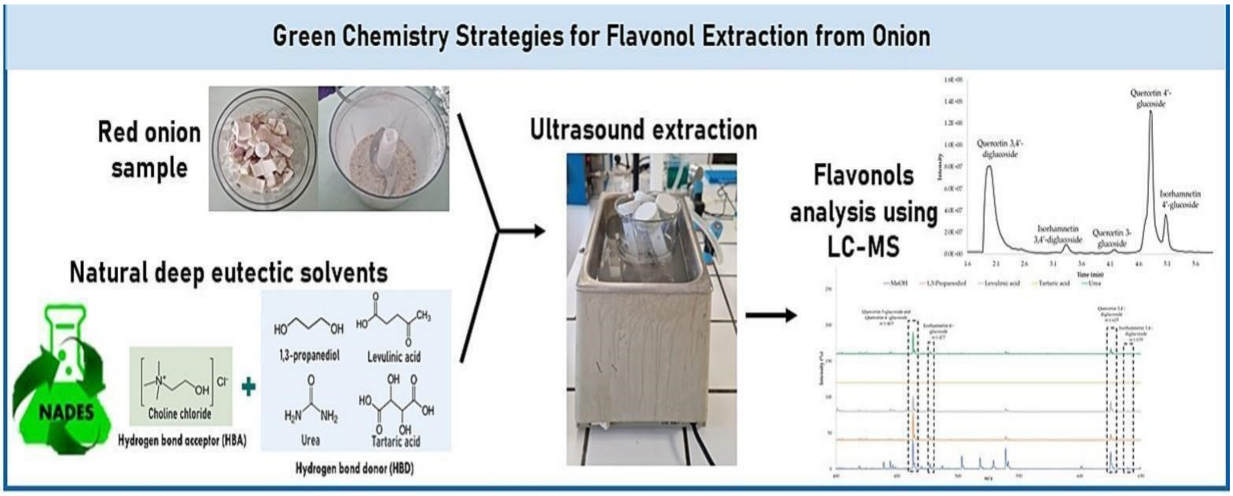

Figure 7: Schematic representation of the protocol for the extraction of red onion flavonols using natural deep eutectic solvents (NaDES) assisted by ultrasound and analysis by LC-MS.

4.4. Treatment of Alzheimer's disease

a. The von Auwers method

The von Auwers synthesis mechanism is shown in **Figure 8**. It begins with the bromination of aurone at the double bond, yielding a 1,2-dibrominated compound. Subsequent substitution of bromine by nucleophilic attack of a hydroxide anion results in an α,β-unsaturated ketone, which produces hydroxyflavone by cyclodebromination.

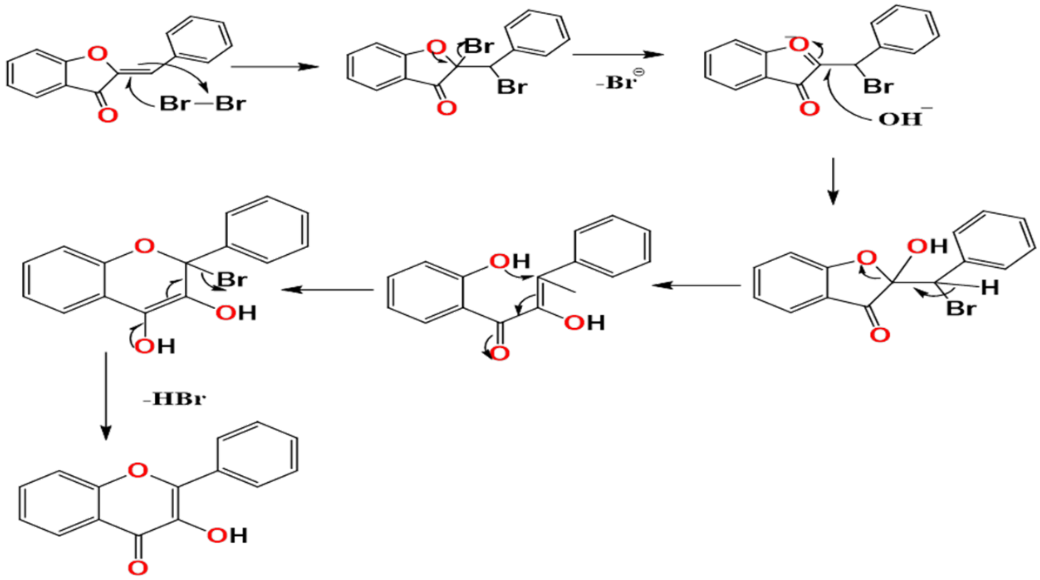

Figure 8: Mechanism of von Auwers synthesis.

Although this method was an improvement over von Kostanecki's, its use in obtaining natural 3hydroxyflavones remained limited. To optimize results, the authors proposed using chlorination rather than bromination. This approach yielded a trichlorinated derivative, which was then converted to a chlorinated hydroxyflavone bearing a chlorine atom at position 5 or 7. However, all attempts to remove the latter chlorine atom failed. Obtaining 3-hydroxyflavones from aurones with better yields was only possible when coumaranone ring cleavage was favored over dehydrohalogenation. The authors finally concluded that the presence of chlorine, methoxy, or methyl groups in position 5 of the coumaranone ring facilitated the formation of 3-hydroxyflavones, while the presence of methoxy or methyl groups in the meta position, as well as two methoxy groups on the aldehyde, made this formation more difficult. (Auwers & Pohl, 1914; Auwers, 1916).

b. Algar-Flynn-Oyamada method.

This method represents the collaboration between Algar and Flynn and the individual work of Oyamada from 1934 to 1935 (**Figure 9**). It can be used to obtain 3-hydroxyflavones from o-hydroxychalcones using hydrogen peroxide in an aqueous solution of sodium hydroxide and cooling (Oyamada, 1935). Algar and Flynn used this method with a hot alcoholic solution of potassium hydroxide, and both obtained good yields (Algar & Flynn, 1934).

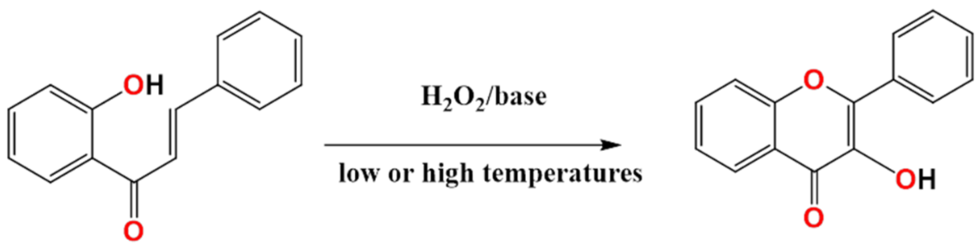

Figure 9: The Algar-Flynn-Oyamada method

The mechanism of the Algar-Flynn-Oyamada reaction has been revised many times over the years (**Figure 10**). Initially, Algar and Flynn suggested the transient formation of ethylene peroxide during the first oxidation step (Algar & Flynn, 1934), although they were unable to isolate any intermediates. Subsequently, Oyamada postulated the existence of a flavanone intermediate, resulting from an electrophilic attack of hydrogen peroxide on position 3 of the flavanone anion. (Oyamada, 1935) (Serdiuk, *et al.*, 2014). However, the work of Dean and Podimuang subsequently refuted the formation of epoxides as intermediates in the production of 3-hydroxyflavones (Dean & Podimuang, 1965)

5. Biological activities of flavonols:

The strong interest in flavonols is mainly due to their antioxidant activity (Crozier, *et al.*, 2000). Flavonols offer exceptional protection against oxidative stress, thereby limiting cellular damage and reducing the severity of chronic diseases. This ability to trap free radicals also allows them to be used as food preservatives to increase the shelf life and stability of fresh products (Shahidi & Ambigaipalan, 2015). In addition, beyond directly neutralizing radicals, these compounds are capable of regenerating the antioxidant vitamins C and E (Vinson, *et al.*, 1995). The elimination of radical species by flavonols is based on various mechanisms involving hydrogen atom transfer (HAT) and electron transfer (ET) (Liu, 2010). Furthermore, the deprotonation of phenolic hydroxyl groups can promote faster reaction kinetics via a sequential proton loss electron transfer (SPLET) mechanism (Xiao, *et al.*, 2021). The choice of the preferred mechanism ultimately depends on the degree of flavonol deprotonation, although these different processes may occur simultaneously during free radical scavenging (**Figure 11**).

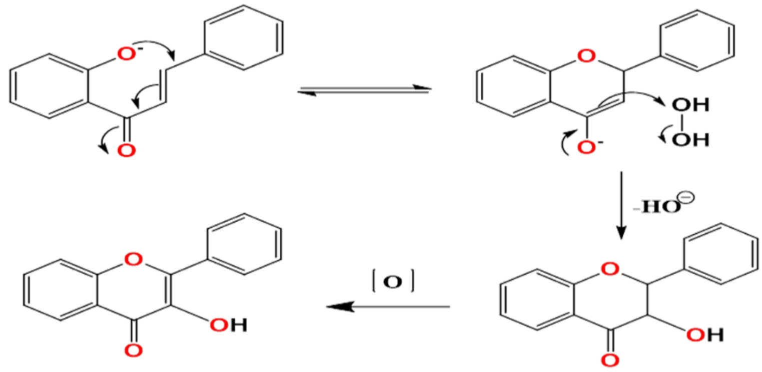

Figure 10: The mechanism of the Algar-Flynn-Oyamada method proposed by Dean and Podimuang

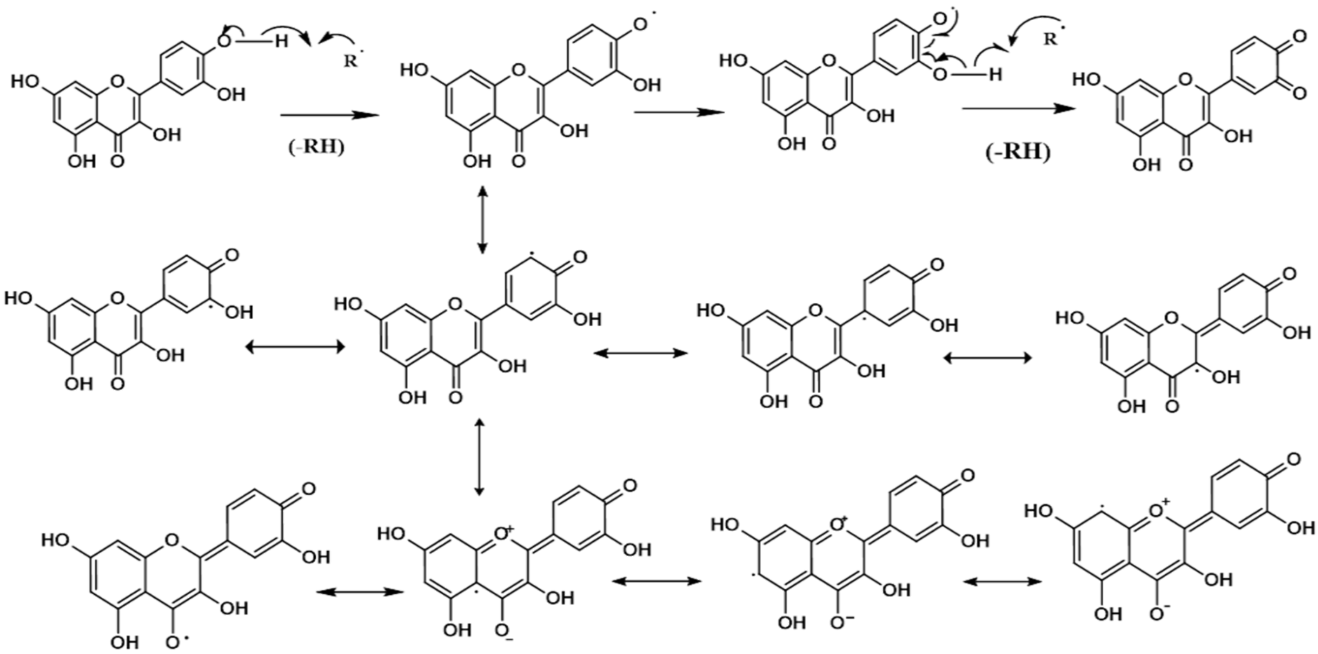

Figure 11: Free radical (R) scavenging mechanism for quercetin

1. Areas of application for flavonols

Flavonols are compounds that have been extensively studied in a variety of scientific fields due to their many biological and chemical properties. Their main application is in agricultural sciences (24.7%). They are also widely used in biochemistry (21.1%) and chemistry (14.8%), where interest focuses on their structure, synthesis, and mechanisms of action. The medical field (9.5%) and pharmacology (11.8%) exploit their potential therapeutic effects, particularly anti-inflammatory, antioxidant, and anticancer properties. Other disciplines such as nursing (2.7%), chemical engineering (3.1%), immunology and microbiology (2.1%), environmental sciences (2.2%) and engineering (1.7%) also incorporate flavonols into their research, demonstrating the growing interest in these compounds. Finally, 6.3% of studies fall into other fields, highlighting the multidisciplinary nature of flavonols (**Figure 12**). It's interesting to indicate that the most cited paper treated the antioxidant acitivity of the range of carotenoids, phenolics, and some plasma antioxidants, determined by the decolorization of the 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid ($ABTS•^{+}$), through measuring the reduction of the radical cation (Re, *et al.*, 1999). It's also noted that more than 97% are articles, reviews and conference papers **(Figure 13)**.

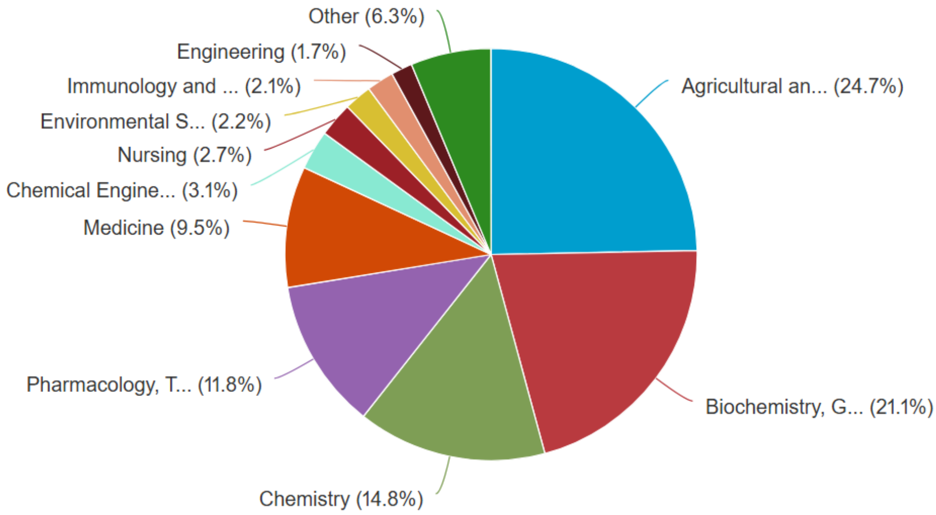

Figure 12: Areas of application for flavonols from Scopus- Elsevier

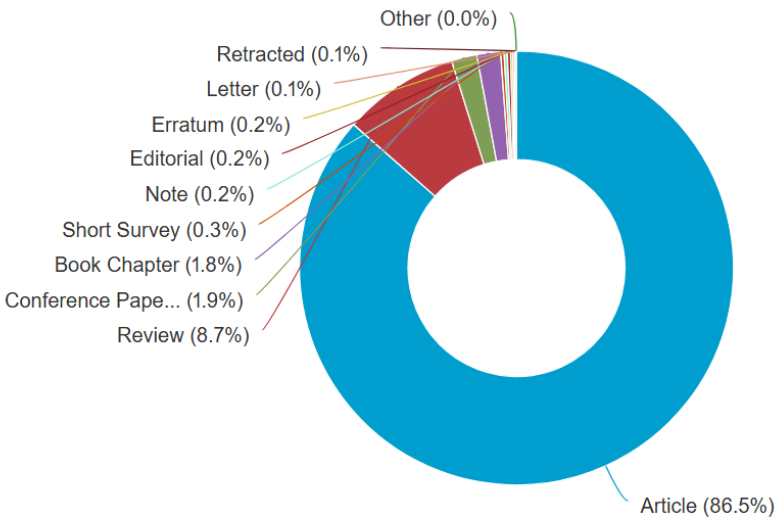

Figure 13: Distribution of type of documents

Flavonols are a family of bioactive compounds with cross-cutting applications, ranging from the food, nutraceutical, and pharmaceutical sectors to the cosmetics and textile industries (**Figure 14**). Their appeal lies in a wide range of rigorously documented functional properties, including their antioxidant, anti-inflammatory, antiviral, antimicrobial, and anticancer activities, as well as their excellent absorption capacity (Barreca, *et al.*, 2021; Ren, *et al.*, 2019; Li, *et al.*, 2019; Kaleem & Ahmad, 2018; Li, *et al.*, 2011; Liu, *et al.*, 2018; Zhou & Tang, 2017; Oualdi *et al.*, 2021, 2023, 2025). In addition, the recovery of many industrial by-products provides a natural, safe, and economical source of these molecules.

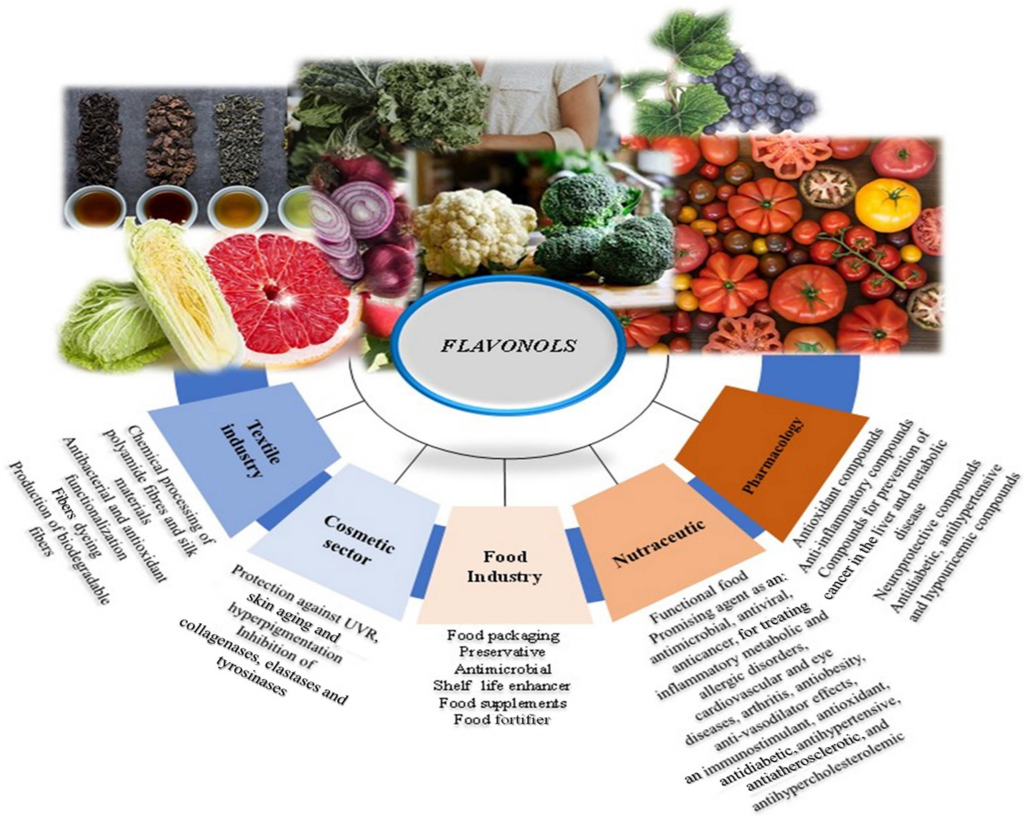

Figure 14: Schematic representation of the main applications of flavonols

Conclusion

Flavonols, an important subclass of flavonoids, occupy a prominent place in the study of natural compounds due to their wide distribution in the plant kingdom and their numerous biological properties. Their common skeleton, based on the 2-phenyl-chromen4-one system, gives them remarkable chemical and bioactive characteristics, such as antioxidant, anti-inflammatory, antiviral, and anticancer properties. These properties make flavonols molecules of interest not only for pharmaceutical and medical research, but also for the food and cosmetics industries. In this work, we have highlighted the structure, natural sources, physicochemical properties, and main methods of synthesis of flavonols. Their abundant presence in common foods such as onions, grapes, and green tea underscores their beneficial role in human health and justifies the growing interest in research in this field. Thus, in-depth study of flavonols contributes to a better understanding of their biological impact and paves the way for new therapeutic or industrial applications.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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