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Review Article

Dietary Flavonols With Antiviral Efficacy: Safety and Regulatory Concerns

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Abstract: Globally, a variety of pharmacologically-active plant or natural products are commonly consumed as health-protective dietary supplements. These are marketed as crude formulations, isolated metabolites, multi-vitamins, essential amino acids, unsaturated fatty acids and minerals. Of these, pharmacologically-active flavonols like rutin, quercetin, kaempferol, myricetin, isorhamnetin are the most consumed dietary supplements. In addition to their broad-spectrum therapeutic benefits, these are also known for good antiviral efficacies in experimental as well as pre-clinical settings. However, though such marketed dietary supplements have gained global popularity, they are generally poorly regulated as compared to conventional drugs for their efficacy and safety. Interestingly, their experimental assessment for non-cytotoxicity as well as clinical evaluation of their intake and mortality risks in a cohort of adults have been recently reported. A comprehensive literature survey was carried out on Google Scholar, PubMed, Europe PMC, Medline and SciHub, using phrases like, herbal or natural dietary supplements, bioactive natural products, dietary flavonols, antiviral natural products, herbal hepatotoxicity and causality, etc. The present article discusses the current knowledge on the marketed dietary flavonols with antiviral efficacy as well as their safety and regulatory measures.

Keywords: Dietary Flavonols, Quercetin, Kaempferol, Myricetin, Isorhamnetin, Safety

Introduction

Physical-inactivity, sedentary life-style, work-pressure and mental-stress together with consumption of junk foods have significantly affected human health. Therefore, to compensate nutritional deficiencies, bioactive natural products or nutraceuticals are commonly consumed as dietary supplements for health protection (Ahmed et al., 2022) These are marketed plant and animal crude-products or mixed-formulations, isolated secondary metabolites, multi-vitamins, essential amino acids, unsaturated fatty acids and minerals (Frey et al., 2017). Health-protective natural or plant products have several benefits over conventional therapeutic regimens for their:

(i) Availability as dietary supplements
(ii) Cost-effectiveness
(iii) Easy intestinal-absorbance
(iv) Effectiveness for home-care patients
(v) Presumed rare side-effects. According to the United States' Food and Drug Administration (FDA) estimation, over 29,000 different dietary supplements have been consumed by ~68% individuals (Sarubin, 2000)

Bioactive flavonoids are plant secondary metabolites, abundantly present in commonly consumed fruits, vegetables and beverages (Samanta et al., 2011). Phytochemically, flavonoids are a class of polyphenols consisting of flavan nucleus with a 15-carbon skeleton and two benzene rings joined by a heterocyclic pyran ring. (Fig. 1). Further, according to variations in their heterocyclic carbon-ring, flavonoids are sub-classified as flavonols, flavanones, flavones, isoflavones, flavonolignans, and flavonoid glycosides, including chalcones, anthocyanidins and catechins (Hollman, 2004).

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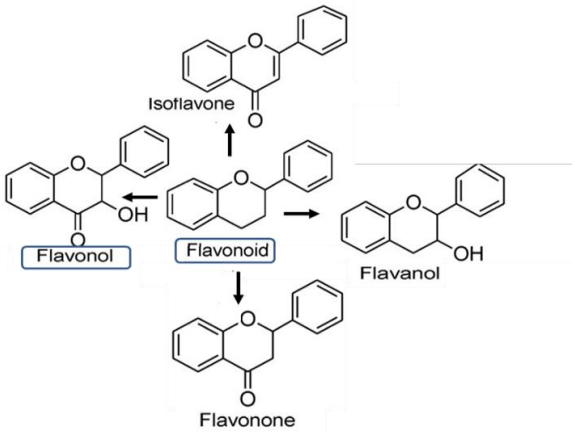

Fig. 1: Structural illustration of flavonoids

Viruses are obligate microbial parasites comprised of genomic nucleic acid (RNA or DNA) and lipid-protein (s) that must invade and hijack live cells machinery to perpetuate. In past decades, many incidences of viral diseases have led identifications of several highly pathogenic viruses of Flaviviridae, Hepeviridae, Paramyxovirida, Coronaviridae, Arenaviridae, Bunyaviridae, Filoviridae and Togaviridae etc. Periodic emergence or re-emergence viral diseases have greatly impacted public health and economy (Parvez and Parveen, 2017). Of these, the early twentieth century Spanish Flu caused by Influenza Virus (INV) was the most devastating pandemic followed by the1957 Asian Flu and the 1968 Hong Kong Flu, responsible for millions of deaths. In recent times, while re-emergence of Swine Flu claimed thousands lives, the epidemic of novel severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) caused hundreds of deaths worldwide. Further, in 2013, a novel Bird Flu in China and the Middle-East Respiratory Syndrome Corona Virus (MERS-CoV) were discovered. Notably, the year 2015 was threatened by the re-emergence of the Ebola virus, and 2015-2016 was challenged with the resurgence of the Zika Virus (ZIKV) (Parvez and Parveen, 2017) and, the most recent emergence of severe acute respiratory syndrome virus-2 (SARS-CoV2) pandemic has devastated human health and global economy (World Health Organization, 2020).

Globally, a range of active viral diseases caused by Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), herpes simplex virus (HSV), Dengue Virus (DNV), Influenza Virus (INV), Chikungunya Virus (CKV) and ZIKV, as well the current the SARS-CoV2 disease (COVID-19) remain serious public health issues (Parvez and Parveen, 2017; Parvez et al., 2020a). Nonetheless, despite rigorous biomedical research in the understanding of the evolution, pathobiology and the breakthroughs in preventions and therapeutics, novel pandemic viruses still pose a great challenge.

In the present article, we have conducted a comprehensive literature survey on online portals such as Google Scholar, PubMed, Europe PMC, Medline and SciHub, using phrases like, herbal or natural dietary supplements, bioactive natural products, dietary flavonols, antiviral natural products, herbal hepatotoxicity and causality, etc., and discuss the current knowledge on the marketed dietary flavonols with antiviral efficacy as well as their safety and regulatory measures.

Pharmacological or Health-Protective Activities of Dietary Flavonols

Pharmacologically-active Flavonols like rutin, quercetin, kaempferol, myricetin, isorhamnetin as well as catechins are the most abundant flavonoids (Samanta et al., 2011; Hollman, 2004) present in onions, berries, nuts and tea, and are commercialized as dietary supplemental pills and tablets in market (Fig. 2). The therapeutic benefits of these flavonols include improvement of cardiovascular function and maintaining endothelial nitric oxide, enhancement of lipid and glucose metabolism, stabilization of blood pressure, enrichment and functionalization of blood-platelet and thrombosis, as well as amelioration of tissue inflammation and oxidative stress (Perez-Vizcaino and Duarte, 2010; Al-Dashti et al., 2018). Also, several flavonoids can induce tumor-specific apoptosis and prevent metastatic cell growth (Zhou et al., 2022), as well as have neurological benefits (Holland et al., 2023). In addition, several of such flavonoids have potent antibacterial and antifungal activities (Friedman, 2007).

Fig. 2: Examples of some marketed dietary flavonoids and flavonols

Pathogenic Human Viruses

Viruses are obligate microbial parasites comprised of genomic nucleic acid (RNA or DNA) and lipid-protein(s) that must invade live cells and hijack host-machinery to perpetuate. Over the past several decades, incidences of viral infections have led to the discovery of a diverse

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range of highly pathogenic viruses belonging to the Arenaviridae, Bunyaviridae, Coronaviridae, Filoviridae, Flaviviridae, Hepeviridae, Paramyxoviridae, and Togaviridae families. Periodic incidences of emerging or re-emerging viral diseases have significantly affected human health and economy (Parvez and Parveen, 2017). Of these, the early twentieth century Spanish Flu caused by Influenza Virus (INV) was the most devastating pandemic followed by the1957 Asian Flu and the 1968 Hong Kong Flu, responsible for millions of deaths. In recent times, while re-emergence of Swine Flu claimed thousands lives, the emergence of a novel Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV) caused hundreds of deaths worldwide. Further, in 2013, a novel Bird Flu in China and the Middle-East Respiratory Syndrome Corona Virus (MERS-CoV) were identified. Notably, the year 2015 was threatened by the re-emergence of the Ebola virus, and 2015-2016 was challenged with the resurgence of the Zika virus (ZIKV) (Parvez and Parveen, 2017). And, the most recent emergence of severe acute respiratory syndrome virus-2 (SARS-CoV2) pandemic has exerted a big toll on public health and world economy (World Health Organization, 2020).

Globally, a range of active viral diseases caused by Herpes Simplex Virus (HSV), hepatitis B virus (HBV), Hepatitis C Virus (HCV), Influenza Virus (INV), Human Immunodeficiency Virus (HIV), Chikungunya Virus (CKV), dengue virus (DNV) and Zika Virus (ZKV), as well the current SARS-CoV2 disease (COVID-19) remain serious public health issues (Parvez and Parveen, 2017; Parvez et al., 2020b). Nonetheless, despite substantial research advancements in the understanding of the biology, evolution, pathogenesis, and the breakthroughs in preventions and therapeutics, novel pandemic viruses still pose a great challenge.

Antiviral Herbal or Natural Products

As an alternative to conventional drugs, a variety of herbal crude-formulations as well as purified bioactive compounds of different phytochemical classes such as alkaloids, terpenes, lignans, flavonoids, polyphenols and anthraquinones etc. are demonstrated as potential anti-viral agents (El Sayed, 2000). Owing to the diverse chemical and structural diversity as well as functional specificity of bioactive plant secondary metabolites or natural compounds, their efficient delivery through various formulations and delivery modules have been used over traditional formulations for enhanced solubility, absorption, bioavailability and improved antiviral activities (Ahmed and Parvez, 2023). Of these, nanogel and mixed micelles or cocrystal delivery of myricetin for INV and HIV; chito-oligosaccharide formulations for INV; microemulsion, mixed micelles, phospholipid-phytosome for against HCV, enterovirus and INV are excellent examples. Several recent studies have reported the effectiveness of herb-synthesized silver nanoparticles (AuNP) antiviral drugs against HIV, INV, and DNV. Furthermore, the glycan-functionalized AuNP has been shown to inhibit INV entry through host cell membrane. Notably, the herbal formulation Honokiol used in traditional Chinese medicine (TCM) has been delivered as conjugate micelles-nanoparticles against HCV and DENV infections (Ahmed and Parvez, 2023).

Dietary Flavanols With Potent Antiviral Properties

With their broad therapeutic-spectrum, several flavonoids, including dietary flavonols have been demonstrated for potent antiviral efficacies in experimental, pre-clinical and clinical studies (Zakaryan et al., 2017; Wang et al., 2020; Badshah et al., 2021). Here, we have discussed the structurally-related and most consumable dietary falvonols *viz*, rutin, quercetin, kaempferol, myricetin and isorhamnetin (Fig. 3), including their derivatives with known antiviral properties in experimental conditions.

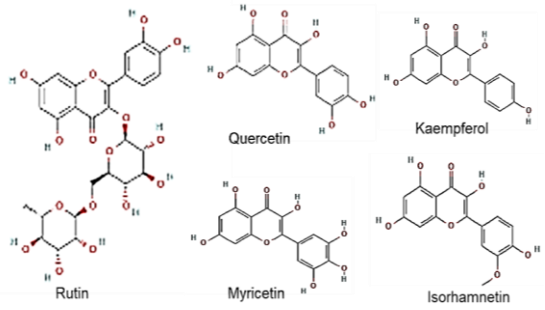

Fig. 3: Structurally-related dietary flavonols (https://pubchem.ncbi.nlm.nih.gov) with antiviral properties

Rutin: Rutin (quercetin-3-O-rutinoside or sophorin) is a well-known pharmacologically-active flavonol (biflavonid), identified as potent antiviral compound against avian INV (H5N1) *in vitro* (Ibrahim et al., 2013; Chéron et al., 2015). Recently, we have also shown its potent anti-HBV activity in cultured hepatoma cells (Parvez et al., 2019).

Quercetin: Quercetin (sophoretin, meletin or xanthourine), the aglycon (non-glycosylated) form of rutin is reported for its marked activities against HIV, HSV, parainfluenza type 3, meningovirus, pseudorabies virus, respiratory syncytial virus (RSV) and Sindbis Virus (SNV) *in vitro* (Mucsi,1984; Kaul et al., 1985; Choi et al., 2009a; Kelly, 2011; Chiow et al., 2016). Interestingly, the enhanced anti-HIV effects of quercetin derivatives by its glycosyl moieties have been also suggested (Ortega et al., 2017). In line with this, considerably higher anti-HSV and anti-HIV potential of quercetin-3-glycoside has been demonstrated (Olivero-Verbel et al., 2002). Also, its

marked anti-HBV efficacy has been shown in cell culture models (Parvez et al., 2019; Cheng et al., 2015; Tsukamoto et al., 2018). Further, the anti-INV efficacy of quercetin-3-rhamnoside has been also demonstrated (Choi et al., 2009b). Moreover, its derivatives quercitrin-3-glucuronide and quercitrin-3-rhamnoside have been also demonstrated for anti-HBV activities (Parvez et al., 2022).

Kaempferol: Kaempferol (robigenin or populnetin), a pharmacologically-active dietary flavonol has been reported as a broad-spectrum antiviral compound against enterovirus, INV, Japanese Encephalitis Virus (JEV), DNV and HSV (Zhang et al., 2012; Dai et al., 2019; Care et al., 2020). Further, its derivatives kaempferol-3-rhamnopyranoside and kaempferol-7-glucoside have been shown for potent anti-INV (Ha et al., 2014) and anti-HIV (Behbahani et al., 2014) activities, respectively. Also, its rhamnose derivatives are shown for promising anti-coronavirus effects (Schwarz et al., 2014). Furthermore, both kaempferol and its derivative kaempferol-3-acetylrhamnoside have been demonstrated for marked anti-HIV activities (Min et al., 2001; Yang et al., 2017). It's another derivative, kaempferol-3,7-bisrhamnoside has been also shown for its potent anti-HCV activity (Dabeek and Marra, 2019). In addition, while kaempferol has been reported for marked in vitro anti-HBV activity elsewhere (Wu, 2016), we have further demonstrated anti-HBV potential of its derivatives kaempferol-3-glucuronide in cultured cells (Parvez et al., 2021).

Myricetin: Myricetin (myricetol or cannabiscetin) is structurally-related to quercetin and kaempferol, which also exists as glycoside derivatives (Semwal et al., 2016). Myricetin is shown for its anti-HBV potential (Yarmolinsky et al., 2012; Pasetto et al., 2014), Interestingly, the glycosylated derivatives of myricetin are shown to further improve tits antiviral efficacies against HIV and HSV (Ortega et al., 2017; Olivero-Verbel et al., 2002). Also, myricetin-3-rhamnoside has been shown to have antiviral efficacies against HIV (Rashed et al., 2012) and HCV (Calland et al., 2014). Moreover, myricetin-3-rhamnoside has been also reported for its *in vitro* anti-INV (H1N1) (Motlhatlego et al., 2018) as well as anti-HSV and anti-Fowl Pox Virus (FPV) (Ficarra et al., 1997) effects. In line with his, we have also reported its strong anti-HBV effect in cultured cells (Parvez et al., 2020a).

Isorhamnetin: Structurally, isorhamnetin (isorhamnetol or 3-methylquercetin) has an additional 3'-methyl group as compared to quercetin and kaempferol. Comparatively, information on antiviral potential of isorhamnetin remains limited. Nonetheless, its in vitro activity against INV has been previously reported (Dayem et al., 2015), Further, we have recently shown its *in vitro* anti-HBV therapeutic potential (Parvez et al., 2022).

Miscellaneous: In COVID-19 patients, some traditional Chinese medicine (TCM) rich in quercetin and kaempferol, including other bioactive flavonoids (naringenin, wogonin luteolin and baicalein) also showed curative effects via exerting direct anti-SARS-CoV2 activities as well as through anti-inflammatory and immune-regulatory mechanisms (Huang et al., 2020).

Safety and Regulatory Measures

Generally, consumption of dietary supplement, mainly the phytoproducts are considered to be more efficacious and safer as compared to the conventional medications. However, in recent times, marketed natural or herbal products-associated adverse effects have been clinically identified in a proportion of consumers (Ahmed et al., 2022; Ronis et al., 2018; Parvez et al., 2019). Notably, adverse side-effects of high flavonoid intake have been also observed in some clinical settings (Skibola and Smith, 2000). The efficacy and safety and overall quality of marketed herbal dietary supplements can be compromised by several factors *viz.*, contents of multi-ingredients, unwanted additives, impurities, chemical adulterations, as well as processing and storage methods. Therefore, their stringent regulation by food-drug and health authorities are necessary prior to commercialization. Notably, herbal dietary supplements are now under regulations of the United States Dietary Supplement Health and Education Act (DSHEA) and FDA, but not as stringently as conventional drugs (Bailey, 2020). Further, the Dietary Supplement and Nonprescription Drug Consumer Protection Act (NDCPA) has also directed the pharma companies to produce pre-clinical reports on any clinical effects of their marketed products to the FDA (Knapik et al., 2022). However, in other countries, such guidelines either remain unregulated or implemented nominally (Ahmed et al., 2022).

In view of this, in our all-reported anti-HBV studies, we have tested all such flavanols and their derivatives for non-toxicity at concentrations up to 200 □g/ml, using cultured hepatoma cell model to validate their safety (Parvez et al., 2019; 2020; 2021; 2022), warranting their further pre-clinical or clinical assessments. Notably therein, we excluded samples showing even mild cytotoxicity. Very recently, in clinical studies, the relationship between dietary flavonols intake and associated mortality-risks has been analysed in a cohort of American consumers, using the National Health and Nutrition Examination Survey (NHANES) data (Knapik et al., 2022). Therein, in compliance with the NHANES reporting requirements' intricate stratification design, the amount and type of consumed dietary total flavonols, quercetin, kaempferol, myricetin and isorhamnetin have been assessed. Moreover, the available mortality data of the National Death Index (NDI) were also used to estimate the 'mortality from all causes' as compared to

'cause-specific' cases of cardiovascular and Alzheimer's diseases, diabetes as well as cancer in over 11,500 non-hospitalized subjects. Conclusively, the study presented no mortality-risks associated with increased flavonols intake, suggesting their anti-tumor, anti-inflammatory, and anti-oxidative therapeutic salutations (Zong et al., 2024). Also, the study showed that while total flavonols intake was markedly related to decreased 'all-cause mortality' risk., consumption of total flavonols, quercetin, kaempferol, and isorhamnetin were associated with lower 'cancer-specific' mortality-risk. On the other hand, total flavonols, quercetin and myricetin intake showed reduction in cardiovascular disease-specific mortality risk. Comparatively, myricetin intake was attributed to lower diabetic mortality risk. Notably, however, there is no such data available on dietary flavonol intake and chronic viral disease-associated mortality risks.

Conclusion

A variety of pharmacologically-active natural or herbal products are commonly consumed as health-supporting dietary supplements commonly sold as crude-products or mixed-formulations, pure metabolites, multi-vitamins, essential amino acids, unsaturated fatty acids and minerals. In general, consumption of plant-derived dietary supplements or therapeutic products are considered as more effective and safer as compared to conventional or prescription drugs. Further, such therapeutic agents are commonly reported for their efficacies but with some CC/IC_{50} values showing their cytotoxic effects above certain dose. When consumed regularly or in high amount, they cause serious side-effects or acute hepatotoxicity. In recent decades, several reports on the adverse-effects and mortalities, associated with such products have been reported. This exists as a serious public health issue with broad implications for dieticians, nutritionists, clinicians and pharma industries as well as health and food-drug authorities. Of the marketed dietary supplements, pharmacologically-active falvonols viz., rutin, quercetin, kaempferol, myricetin and isorhamnetin, including their derivatives are also known for their promising antiviral properties. However, studies on their broad-spectrum antiviral potential remain restricted to experimental and pre-clinical levels. Notably, though such marketed products have gained global popularity, they are hitherto, poorly regulated as compared to conventional drugs for their efficacy and safety in general. Interestingly, in addition to their experimental assessment for non-cytotoxicity, the intake of such flavonols have been also evaluated in a cohort of adult consumers for their health benefits and mortality risks. Nonetheless, the reportedly significant antiviral efficacies of these dietary flavonols against several human viruses convincingly warrant their pre-clinical and clinical studies.

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Author's Contributions

Mohammad Khalid Parvez: Conceived, planned and prepared the final draft of the manuscript.

Tanisha Parvez and Tanveer Yaqub: Searched literature and collected.

Shama Parveen: Reviewed and prepared the final manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all authors have read and approved the manuscript and no ethical issues are involved.

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