Open Access

Recent Progress in Nutrition

LIDSEN Publishing Inc.

Review

Nutritional Health and Bioflavonoids

Harald P. Hoensch [1], Benno Weigmann [2, 3, *]

1. Retired internist Marienhospital Darmstadt, Consultant, University of Erlangen-Nuremberg, Germany; E-Mail: h.p.hoensch@t-online.de
2. Department of Medicine 1, University of Erlangen-Nuremberg, Kussmaul Campus for Medical Research, Erlangen, Germany; E-Mail: Benno.Weigmann@uk-erlangen.de
3. Medical Immunology Campus Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany

* **Correspondence:** Benno Weigmann; E-Mail: Benno.Weigmann@uk-erlangen.de

Academic Editor: Rafat A. Siddiqui

Special Issue: Role of Diets, Vitamins, and Minerals in Cancers and Various Diseases

Recent Progress in Nutrition
2022, volume 2, issue 3
doi:10.21926/rpn.2203017

Received: March 23, 2022
Accepted: July 13, 2022
Published: July 21, 2022

Abstract

Flavonoids are phytochemicals (polyphenols) of plant origin. They can trap free oxygen radicals generated by mitochondria and other electronic transport chains, thereby inhibiting inflammatory and carcinogenic changes in vivo and in vitro. Why the body requires these compounds for the well-being of the organism and the maintenance of human health remains unclear. However, a deficit of flavonoids could lead to molecular malfunctions in cells, organelles, and macromolecules. This manuscript describes the occurrence and prevalence of flavonoid exposure in some chronic inflammatory diseases and their relationship with each other.

Keywords

Flavonoids; apigenin; EGCG; nutritional supplements; food; dietary intake

1. Introduction

Flavonoids are phytochemicals (polyphenols) of plant origin. They can trap free oxygen radicals generated by mitochondria and other electronic transport chains, thereby inhibiting inflammatory and carcinogenic changes in vivo and in vitro. Why the body requires these compounds for the well-being of the organism and the maintenance of human health remains unclear. However, a deficit of flavonoids could lead to molecular malfunctions in cells, organelles, and macromolecules. This manuscript describes the occurrence and prevalence of flavonoid exposure in some chronic inflammatory diseases and their relationship with each other.

2. Flavonoid Sources

More than 4000 flavonoid species have been characterized, and they exhibit a wide variety of chemical structures; the generic structure is illustrated [1, 2] in Figure 1. They are absorbed by the intestinal mucosa of the jejunum through an active energy-dependent pathway; the absorption is similar to that of cytochrome P-450 and conjugated drugs [3]. While being absorbed through the mucosa, these xenobiotic compounds are enzymatically metabolized to water-soluble products that are distributed, excreted, and eliminated from the human body. Flavonoids can sometimes act as drugs depending on their chemical structure. For humans, the main sources of flavonoids are plant food, especially vegetables, fruits, berries, and legumes.

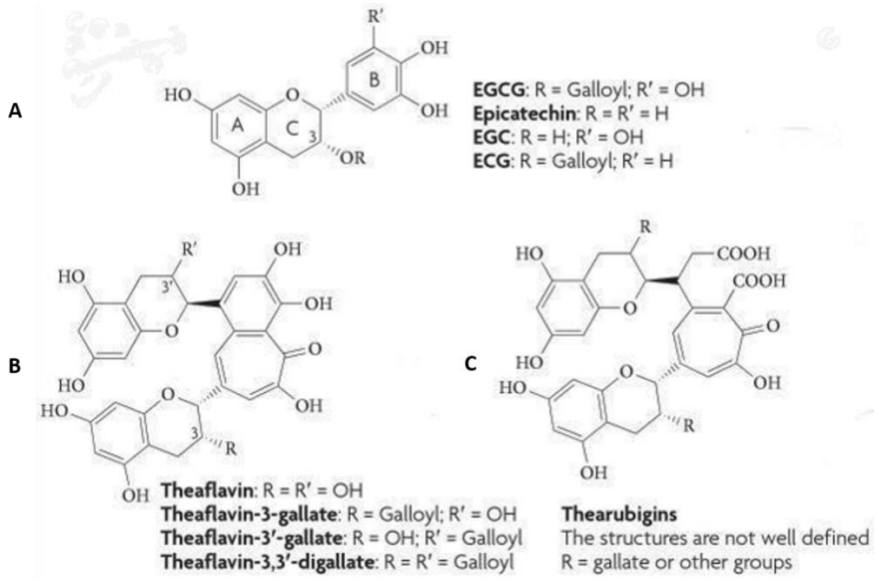

Figure 1 Generic structure of common flavonoids. (A) Flavonoids share a common structure consisting of two aromatic rings (ring A and ring B) that are bound together by three carbon atoms forming an oxygenated heterocycle (ring C). This results in a typical C6-C3-C6 flavan backbone, which is the precursor of all flavonoids and contains two phenyl rings. (B) Structural formula of theaflavins and their modifications. They are produced by oxidative condensation between epicatechin and epigallocatechin and are responsible for the typical reddish-orange color of black tea. (C) Structural formula of thearubigins that are polymeric polyphenols and are produced by oxidative condensation between epigallocatechin and epigallocatechin gallate during black tea fermentation. They are responsible for the typical red color.

All flavonoids originate in plants and are classified into 6 major subgroups, namely flavonols, flavones, flavanols, flavanones, anthocyanidins, and isoflavonoids [4]. Flavonoids are ubiquitous in plants and represent the most common secondary plant metabolites in angiosperms. They are responsible for providing colors to flowers, leaves, and other aerial plant parts. The flavonoid content in different plant species varies enormously [5]; the variation is observed even within one plant species and is influenced by internal and external factors. The internal factors are the genetic constitution and the ripeness of edible plant parts at harvesting, whereas the external factors include the cultivation technique (conventional or ecological), fertilization, and climate during the growth period [6]. Flavanones are characteristic of citrus fruits [7], whereas flavones are mostly present in umbelliferous plants [8]. Higher amounts of isoflavones can be detected in legumes, such as soybeans [9]. Flavanols are mostly found in tea, red wine, and fruits, whereas anthocyanidins are present in stone and soft fruits [5]. Most of the flavonoids found in edible plant parts, such as fruits (grape, plums, and different soft fruits), vegetables (curly kale, aubergine, and onions), herbs, tea, and cocoa, are glycosides, with the exception of flavanols (catechins) [10]. The glycosylated form favors flavonoid solubility in the plant and protects them from light and enzymatic degradation [10]. In addition, many edible medicinal plants (such as *cirsium japonicum*, *dillenia suffruticosa,* and *citrus reticulata*) and traditional Chinese medicine formulas like HQT (Huangqin Tang) [11] are rich in flavonoids, some of which have been successfully used in human health management or clinical treatments [12].

Flavonol intake was first calculated by the Seven Countries Study, which was started in the late 1950s; they reported that tea is the major source of quercetin in the Netherlands and in Japan [13]. Onions and apples are the predominant flavonol sources in the United States, Finland, and Greece, whereas red wine is the predominant source in Italy. Vine and tea have a high flavonoid content of up to 45% and are referred to as the "king of flavonoids" as well as *Ginko biloba* [14–16].

The total daily amount of flavonoids in the average Western diet ranges from 200–1000 mg/day and goes down to 144 mg/day in patients with inflammatory bowel disease (IBD) [17]. Teas like green tea and chamomile are the major sources of dietary flavonoids and contain 200–300 mg of apigenin (chamomile) and epigallocatechin gallate (EGCG) [18, 19]. Several studies have focused on the effects of flavonoid intake on healthy individuals (Table 1) and patients with IBD (Table 2).

Table 1 Dietary Average Intake of Flavonoids in Groups (cohorts) With Normal Pathology.

Compound	Class	Function	Source in Nature	Intake
Total Intake [20]	Food, prospective	cohort with adults, NHANES study	Tea, Wine, Beer, Citrus-Fruits	345 ±9 mg/day
			Flavan-3-ol	192 ±7 mg/day
Total Intake [21]	Food [1] Dietary [2] prospective	1. Danish study with 57,053 cohort for prevention of peripheral artery disease	tea, chocolate, wine, apples, pears	174 mg/day
Total Intake [22]		2. Danish study with 56,048 cohort		116 mg/day

EGCG [23]	Flavanols	antioxidants	Tea, Fruits, Cacao, Camellia sinensis	10 mg/day [3]
Quercetin [24]	Flavonols	IBD-model, anticarcinogen	Onions (25 mg/100 g)	16 mg/day
Apigenin [25]	Flavones	Anti-neoplastic	camomile, parsley, celery	2–3 mg/day
Naringenin [26]	Flavanons	Source of Ballast	Citrus fruits	3 mg/day
Anthocyanidins [27]	Cyanidin	Wine	Blue Berries, fruits	15 mg/day
Total Intake [28]	habitual intake of flavonoid subclasses (flavonols, flavones, flavanones, flavan-3-ols, and antho-cyanins)	Professional health study with men: 42.478, woman: 76.362 cohort	Study for prevention of colorectal cancer with 2516 patients	107–808 mg/day mean range: 267 mg
Total Intake [29]	Case-controlled habitual intake	Observational and questionnaires	Bellvitge Colorectal Cancer Study	161–428 mg/day mean range: 199 mg mg/day
Total Intake [30]	US Adults habitually intake	HEI-Score [4] Cohort with 5420 adults	Tea	mean range: 275 mg/day
Review of epidemiological studies linking PA consumption and health reservation [31]	PA (Pro-anthocyanidins, Flavan-3-ol)	Prebiotics	grapes, cocoa, chocolate, red wine, and green tea, but other fruits and vegetables	90–300 mg/day

[1] Danish cohort study max. 494 g/day, prospective observational study with proportional Cox regression. Hazard risk analysis. [2] Habitational individual diet. [3] Without oligomers or polymers. [4] HEI-score: Healthy eating index.

Table 2 Dietary Average Intake of Flavonoids in patients with Inflammatory Bowel disease.

Intake groups (cohorts)	**Males**	**Females**	**CD**	**UC**
Combined study with 204 cohort and 1008 mg/day intake [32]	N = 113 882 mg/week	N = 91 1111 mg/week *	N = 126 153 mg/week (severe score)	N = 78 420 mg/week ** (severe score)

Total Intake of MPFF [1] [17]	144 mg/day	147–260 mg/day

* Significantly higher than men; ** significantly higher than CD group; [1] micronized purified flavonoid fraction, 1000 mg/day.

3. Molecular Mechanisms of Flavonoids (Role of Ah-Receptor)

Tea flavonoids stimulate the protective enzymes of the gastrointestinal tract, thereby improving the intestinal mucosal barrier of the gut epithelial layer that metabolizes toxic and carcinogenic chemicals. Flavonoids bind sequentially to the extracellular angiotensinogen receptor (ACF2) and to the intracellular Ah-receptor complex, which mediates the expression of beneficial target genes. On a cellular level, the inflammatory activities of cytokines and chemokines of the immune system are inhibited by the complementary action of apigenin and EGCG. Both humoral response and innate cellular immune reaction are suppressed. Regarding the effects on pathophysiology, flavonoids may act as mild cytostatic drugs helping to curb chronic toxic, inflammatory, and precarcinogenic conditions. Tumor prevention by flavonoid treatment is feasible; however, it is yet to be demonstrated in cell culture models.

4. Clinical Evidence for Flavonoid Efficacy

Several clinical studies have indicated that age, precancerous and cancer conditions, chronic IBD as well as neurodegenerative disorders, such as Alzheimer's, multiple sclerosis, and Parkinson could be associated with a dietary deficiency of flavonoids. Several huge Denmark-based epidemiological studies have suggested that the total morbidity and mortality related to cancer, chronic cerebrovascular disease, IBD, and neurodegenerative disease can be reduced through a high dietary flavonoid intake.

The results of epidemiological studies concerning the efficacy of flavonoids in cancer prevention are contradictory. Some studies could not identify any association between the consumption of secondary plant metabolites and the risk of cancer, whereas other studies demonstrated a lower incidence of cancer in people consuming diets rich in edible plants [8]. For instance, some studies have revealed that higher isoflavone intake through soy products is inversely related to the incidences of several cancers, such as breast, prostate, and colon, as well as to the incidences of inflammation-mediated chronic diseases [33]. Initial studies have focused on the radical scavenging and radical suppressing capacities of these plant-based substances; however, subsequent experimental and observational studies have suggested that apart from their antioxidative capability, other mechanisms of action may be responsible for their protective effects [34]. Various laboratory investigations have demonstrated the interaction potential of flavonoid subclasses with different enzyme systems, transport proteins, cell adhesion, or heat shock proteins; their capability to simulate hormones or neurotransmitters; and their effects on gene expression [33].

Flavonoids can improve overall health status. In prospective cohort studies, an increased flavonoid uptake in study populations resulted in a decrease in the cumulative incidence rate of intestinal neoplasia. Therefore, future clinical trials should be conducted on patients who are continually treated with oral flavonoids as a preventive therapy. In addition, flavonoids may even play a positive role in the suppression of coronavirus [35]. Recent studies have reported that

Ampelopsis grossedentata has a high content of flavonoids, which act as covalent inhibitors of SARS-CoV-2 $3CL^{pro}$ [36, 37].

5. Flavonoid Exposure through Nutritional Supplements

Flavonoids are common in nature, but they are only available in some plants [12]. Most flavonoids are present in foods, such as vegetables, fruits, drinks, teas, and food supplements (FS) [38]. The administrative supervision of FS is performed by the state government, and the quality of the product is guaranteed by the manufacturer. No Food and Drug Administration (FDA) approval is necessary. FS can help patients to experience their own results without interference from medical providers and to navigate the follow-up. Individuals using FS are responsible for their treatment. Exposure under real-life conditions in observational studies is a valuable tool to take responsibility for their treatment outcomes. However, detailed information on flavonoids is required.

6. Pharmacological Properties and Galenic Description of Tea Flavonoids

The main sources of flavonoids are natural compounds that are harvested commercially from whole plants (chamomile and EGCG). Flavonoid infusates are organic and are freeze-dried and stored [39]. The raw material is bottled and confectioned into gelatin capsules.

The ingredients and content of the ready-to-swallow capsules are provided below. One capsule of Flavo-Natin (0.85 g FN) contains the following flavonoids (200 mg dried extract from green tea and chamomiles):

Component	Amount
Apigenin-7-Glucosid	10.0 mg
Epigallocatechin gallate	10.4 mg
Epicatechin gallate	4.0 mg
Epigallocatechin	2.1 mg
Epicatechin	1.4 mg
Quercetin	0.6 mg
Catechin	0.3 mg
Myricetin	0.2 mg

Additionally, one capsule of FN contains 6 mg caffeine, 55 mg vitamin C, 110 µg folic acid, 1.3 mg vitamin B6, 2 µg vitamin B12, inulin (23%), fructose, cellulose, sorbitol, calcium hydrogen phosphate, magnesium stearate, and lemon flavor.

The recommended daily dose is 2 × 2 capsules (10 mg apigenin and 10 mg EGCG per capsule) taken continually. The capsule can be opened, and the powder can be dissolved in liquids. The water-soluble content results in a clear liquid, but when standing for some time, it turns dark because of polymerization.

To evaluate the effects of flavonoids, their stability should be established. As light-sensitive compounds, flavonoids must be stored in the dark and under dry conditions. The expiry date of these capsules is 12 months. To prevent auto-oxidation, the capsule content is fortified with water-soluble vitamins. The microflora is improved by the addition of inulin, and each capsule contains 6 mg of caffeine.

7. Safety

Flavonoids can inhibit thyroid function, deplete folic acid and vitamin C levels, and inactivate iron and copper ions [23]. The levels of protective enzymes (phase 1 and phase 2), as well as the glutathione complex, are reduced. Clinically, flavonoids inhibit diarrhea in irritable bowel syndrome (IBS) and improve dyspepsia. A dosage of 2 × 2 Flavo-Natin capsules is required for controlling acute symptoms, whereas 2 × 1 was required for preventive therapy in long-term trials (Ethics committee, University of Dresden, Germany).

The product is free of lactose, fructose, and gluten. No bacterial contamination was detected. The content of pyrrholizidine alkaloids (PA) was measured as an indicator of plant toxins. However, only trace amounts of PA were detected [18].

We noted that green tea bags obtained from a commercial supplier does not enter the body, and, therefore, pharmacokinetics could not be established; this indicated the poor bioavailability of EGCG.

The levels of apigenin (subfraction of total level) can be determined in blood serum and serve as a biomarker of flavonoid exposure. We measured apigenin levels after ingestion of 5 flavonoid tablets (Figure 2), each containing a mixture of tea flavonoids, such as apigenin (10 mg), EGCG (10 mg), and other tea flavonoids at a starting concentration.

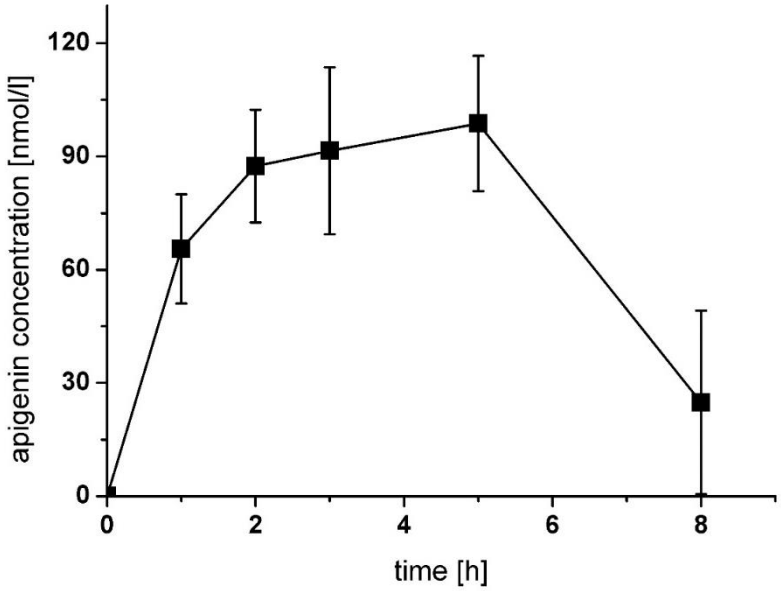

Figure 2 Mean serum concentration of apigenin in a volunteer cohort (n = 6) after ingestion of 5 flavonoid capsules over time. The initial concentration was 10 mg, and the mean concentration was determined in the blood serum at different time points by using enzyme-linked immunoassay (ELISA). The mean values with standard error of the mean (SEM) are provided.

Values for the circulating half-life (T1/2) of apigenin in these studies ranged from 1.84 h to 2 h, with an average value of 2.52 ±0.56 h [40–42]. With systematic dosing, this would translate to a steady state within approximately 12 h. In our work on the downregulation of dipeptidyl peptidase IV (DPPIV) in human colorectal cancer cells by adenosine, it was necessary to use a single dose concentration of 300 µmol/L to produce a robust effect [43].

Our results demonstrated a maximum detectable amount of apigenin at 5 h after ingestion. Given the rapid half-life of agigenin, our overtime result of 40–160 nmol/L indicated that absorption of food flavonoids from a conventional Western diet is not sufficient to provide detectable and quantifiable levels of apigenin. However, measurable exposure to at least apigenin can be found in nutritional supplements, such as tea extracts. The cumulative incidence rates for apigenin can be individualized.

Flavonoids have become a valuable tool in clinical medicine. They serve as health-promoting agents and have been demonstrated to be effective in preventing cancer, chronic IBD, cardiovascular disease, and neurodegenerative disorders. Their activities are mediated by antioxidative, anti-inflammatory, and anticarcinogenic protective enzymes, immune reactive cells, and antibodies.

8. Conclusion

Flavonoids serve as health-promoting agents and prevent cancer, chronic IBD, cardiovascular disease, and neurodegenerative disorders. Therefore, they are considered a valuable tool in clinical medicine. The protective activities of flavonoids are mediated by antioxidative, anti-inflammatory, and anticarcinogenic enzymes. This report highlights the role of bioflavonoids (of plant origin) and their transformation as an essential component of human nutrition. However, these phytochemicals are subject to uptake, absorption, and metabolic pharmacokinetics. The bioavailability of total flavonoids and their subclasses, therefore, depends mainly on nutritional and environmental influences and can best be ensured by dietary supplements (FS). The recommended daily total dietary level is 200–400 mg; however, to maintain this level and to prevent a deficit, a reliable flavonoid carrier is necessary. Therefore, we developed a rational and reliable flavonoid source that was validated by several clinical studies, including a prospective controlled cohort clinical study, an observational controlled study with apigenin level as a biomarker, a pharmacokinetic study in probands, and an analysis of compounds in the flavonoid capsules as well as by using the clinical guidelines of the DGVS.

The usage of flavonoids for therapeutic purposes is best possible when they are applied evidence-based and when they are used as nutritional supplements (FS).

A successful flavonoid therapy can be achieved when the amount and type of dietary flavonoids used correspond to clinical guidelines. Nutritional supplements can bridge the gap between wellness and health and can thus be part of a holistic and integrated approach.

Abbreviations

EGCG	Epigallocatechin gallate
IBD	Inflammatory Bowel Disease
IBS	Inflammatory Bowel syndrome
FS	Food Supplementation
FN	Flavo-Natin
DGVS	Deutsche Gesellschaft für Verdauungs-und Stoffwechselkrankheiten

Acknowledgement

We thank Dr. R. Oertel from the Clinical Pharmacolgy in Dresden for the analytical work on flavonoids. This work was funded by the SFB1181/B02.

Author Contributions

All authors gave the final approval of the version to be submitted.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Weng ZM, Ge GB, Dou TY, Wang P, Liu PK, Tian XH, et al. Characterization and structure-activity relationship studies of flavonoids as inhibitors against human carboxylesterase 2. Bioorg Chem. 2018; 77: 320-329.
2. Wen L, Jiang Y, Yang J, Zhao Y, Tian M, Yang B. Structure, bioactivity, and synthesis of methylated flavonoids. Ann N Y Acad Sci. 2017; 1398: 120-129.
3. Hoensch H, Oertel R. Anti-inflammatorische Wirkungen der Tee-Flavonoide. Dtsch Med Wochenschr. 2012; 137: 2738-2740.
4. Liu RH. Potential synergy of phytochemicals in cancer prevention: Mechanism of action. J Nutr. 2004; 134: 3479S-3485S.
5. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr. 2000; 130: 2073S-2085S.
6. Duthie SJ, Jenkinson AM, Crozier A, Mullen W, Pirie L, Kyle J, et al. The effects of cranberry juice consumption on antioxidant status and biomarkers relating to heart disease and cancer in healthy human volunteers. Eur J Nutr. 2006; 45: 113-122.
7. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: Food sources and bioavailability. Am J Clin Nutr. 2004; 79: 727-747.
8. Böhm H, Boeing H, Hempel J, Raab B, Kroke A. Falvonole, Flavone und Anthocyane als natürliche Antioxidantien der Nahrung und ihre mögliche Rolle bei der Prävention chronischer Erkrankungen. Eur J Nutr. 1998; 37: 147-163.
9. Bravo L. Polyphenols: Chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev. 1998; 56: 317-333.
10. Aherne SA, O'Brien NM. Dietary flavonols: Chemistry, food content, and metabolism. Nutrition. 2002; 18: 75-81.
11. Li T, Zhuang S, Wang Y, Wang Y, Wang W, Zhang H, et al. Flavonoid profiling of a traditional Chinese medicine formula of Huangqin Tang using high performance liquid chromatography. Acta Pharm Sin B. 2016; 6: 148-157.
12. Ullah A, Munir S, Badshah SL, Khan N, Ghani L, Poulson BG, et al. Important flavonoids and their role as a therapeutic agent. Molecules. 2020; 25: 5243.
13. Hertog MG, Kromhout D, Aravanis C, Blackburn H, Buzina R, Fidanza F, et al. Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. Arch Intern Med. 1995; 155: 381-386.

14. Zhao DF, Fan YF, Yu HN, Hou FB, Xiang YW, Wang P, et al. Discovery and characterization of flavonoids in vine tea as catechol-O-methyltransferase inhibitors. Fitoterapia. 2021; 152: 104913.
15. Qin XY, Hou XD, Zhu GH, Xiong Y, Song YQ, Zhu L, et al. Discovery and characterization of the naturally occurring inhibitors against human pancreatic lipase in ampelopsis grossedentata. Front Nutr. 2022; 9: 844195.
16. Chen TR, Wei LH, Guan XQ, Huang C, Liu ZY, Wang FJ, et al. Biflavones from Ginkgo biloba as inhibitors of human thrombin. Bioorg Chem. 2019; 92: 103199.
17. Khryshchanovich VY, Nebylitsin YS, Kosinets VA. Efficacy of micronized purified flavonoid fraction-based venoactive therapy after endovenous mechanochemical obliteration: Prospective comparative study. Drugs Real World Outcomes. 2021; 8: 349-358.
18. Hoensch HP, Weigmann B. Regulation of the intestinal immune system by flavonoids and its utility in chronic inflammatory bowel disease. World J Gastroenterol. 2018; 24: 877-881.
19. Hoensch HP, Zenger R. Pyrrolizidin-Alkaloide in der Nahrung: Der toxikologische Blick – Pyrrolizidin- Alkaloide und Grüne Tees. 2020; 38: 216-219.
20. Bai W, Wang C, Ren C. Intakes of total and individual flavonoids by US adults. Int J Food Sci Nutr. 2014; 65: 9-20.
21. Bondonno NP, Murray K, Cassidy A, Bondonno CP, Lewis JR, Croft KD, et al. Higher habitual flavonoid intakes are associated with a lower risk of peripheral artery disease hospitalizations. Am J Clin Nutr. 2020; 113: 187-199.
22. Bondonno NP, Dalgaard F, Kyrø C, Murray K, Bondonno CP, Lewis JR, et al. Flavonoid intake is associated with lower mortality in the Danish diet cancer and health cohort. Nat Commun. 2019; 10: 3651.
23. Egert S, Rimbach G. Which sources of flavonoids: Complex diets or dietary supplements? Adv Nutr. 2011; 2: 8-14.
24. James MO, Sacco JC, Faux LR. Effects of food natural products on the biotransformation of PCBs. Environ Toxicol Pharmacol. 2008; 25: 211-217.
25. Leonardi T, Vanamala J, Taddeo SS, Davidson LA, Murphy ME, Patil BS, et al. Apigenin and naringenin suppress colon carcinogenesis through the aberrant crypt stage in azoxymethane-treated rats. Exp Biol Med (Maywood). 2010; 235: 710-717.
26. Farzaei MH, Rahimi R, Abdollahi M. The role of dietary polyphenols in the management of inflammatory bowel disease. Curr Pharm Biotechnol. 2015; 16: 196-210.
27. Mena P, Domínguez-Perles R, Gironés-Vilaplana A, Baenas N, García-Viguera C, Villaño D. Flavan-3-ols, anthocyanins, and inflammation. IUBMB Life. 2014; 66: 745-758.
28. Nimptsch K, Zhang X, Cassidy A, Song M, O'Reilly ÉJ, Lin JH, et al. Habitual intake of flavonoid subclasses and risk of colorectal cancer in 2 large prospective cohorts. Am J Clin Nutr. 2016; 103: 184-191.
29. Zamora-Ros R, Not C, Guinó E, Luján-Barroso L, García RM, Biondo S, et al. Association between habitual dietary flavonoid and lignan intake and colorectal cancer in a Spanish case-control study (the Bellvitge Colorectal Cancer Study). Cancer Causes Control. 2013; 24: 549-557.
30. Sebastian RS, Wilkinson Enns C, Goldman JD, Martin CL, Steinfeldt LC, Murayi T, et al. A new database facilitates characterization of flavonoid intake, sources, and positive associations with diet quality among US adults. J Nutr. 2015; 145: 1239-1248.

31. Bladé C, Aragonès G, Arola-Arnal A, Muguerza B, Bravo FI, Salvadó MJ, et al. Proanthocyanidins in health and disease. Biofactors. 2016; 42: 5-12.
32. Kölbel B, Hoensch HP, Hamacher S, Hellmich M, Kruis W. Low dietary flavonoid consumption is associated to severe inflammatory bowel disease. World J Gastroenterol. 2022. [manuscript in preparation].
33. Brandi ML. Natural and synthetic isoflavones in the prevention and treatment of chronic diseases. Calcif Tissue Int. 1997; 61 Suppl 1: S5-S8.
34. Havsteen BH. The biochemistry and medical significance of the flavonoids. Pharmacol Ther. 2002; 96: 67-202.
35. Russo M, Spagnuolo C, Moccia S, Tedesco I, Lauria F, Russo GL. Biochemical and cellular characterization of new radio-resistant cell lines reveals a role of natural flavonoids to bypass senescence. Int J Mol Sci. 2021; 23: 301.
36. Xiong Y, Zhu GH, Wang HN, Hu Q, Chen LL, Guan XQ, et al. Discovery of naturally occurring inhibitors against SARS-CoV-2 $3CL^{pro}$ from ginkgo biloba leaves via large-scale screening. Fitoterapia. 2021; 152: 104909.
37. Xiong Y, Zhu GH, Zhang YN, Hu Q, Wang HN, Yu HN, et al. Flavonoids in Ampelopsis grossedentata as covalent inhibitors of SARS-CoV-2 $3CL^{pro}$: Inhibition potentials, covalent binding sites and inhibitory mechanisms. Int J Biol Macromol. 2021; 187: 976-987.
38. Ross JA, Kasum CM. Dietary flavonoids: Bioavailability, metabolic effects, and safety. Annu Rev Nutr. 2002; 22: 19-34.
39. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: An overview. Sci World J. 2013; 2013: 162750.
40. Wan L, Guo C, Yu Q, Li Y, Wang X, Wang X, et al. Quantitative determination of apigenin and its metabolism in rat plasma after intravenous bolus administration by HPLC coupled with tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2007; 855: 286-289.
41. Chen Z, Ying X, Meng S, Zhu X, Jiang H, Cao Q, et al. High-performance liquid chromatographic determination and pharmacokinetic study of apigenin-7-O-β-D-glucoside in rat plasma after intravenous administration. Arch Pharm Res. 2011; 34: 741-746.
42. Ding SM, Zhang ZH, Song J, Cheng XD, Jiang J, Jia XB. Enhanced bioavailability of apigenin via preparation of a carbon nanopowder solid dispersion. Int J Nanomedicine. 2014; 9: 2327-2333.
43. DeRango-Adem EF, Blay J. Does oral apigenin have real potential for a therapeutic effect in the context of human gastrointestinal and other cancers? Front Pharmacol. 2021; 12: 681477.

Enjoy *Recent Progress in Nutrition* by:

1. Submitting a manuscript
2. Joining in volunteer reviewer bank
3. Joining Editorial Board
4. Guest editing a special issue

For more details, please visit:
http://www.lidsen.com/journals/rpn