Lethbridge Undergraduate Research Journal
ISSN 1718-8482

Lethbridge Undergraduate Research Journal
ISSN 1718-8482

A Review of Potential Health Benefits of Flavonoids

Jay M. Patel
Second year B.Tech (pharmaceutical and fine chemicals technology)
Institute of chemical technology
University of Mumbai
Mumbai, India

Citation:

Jay M. Patel: A Review of Potential Health Benefits of Flavonoids . *Lethbridge Undergraduate Research Journal.* 2008. Volume 3 Number 2.

Table of Contents

Abstract

Flavonoids occur naturally in fruit, vegetables, and beverages such as tea and wine and over 4000 structurally unique flavonoids have been identified in plant sources. Plants and spices containing flavonoids have historically been used in traditional eastern medicine. Research in the field of flavonoids has increased since the discovery of the French paradox i.e. the low cardiovascular mortality rate observed in Mediterranean populations in association with red wine consumption and a high saturated fat intake. The aim of this review is to obtain a further understanding on the reported beneficial health effects of these substances and discuss the action of flavonoids as antioxidants. The major actions of flavonoids are those against cardiovascular diseases, ulcers, viruses, inflammation, osteoporosis, diarrhea and arthritis. Brief description about the disease causing effect of free radicals is given and ways by which flavonoids neutralize free radicals has also been mentioned.

Keywords: Flavonoids, free radicals, antioxidants, French paradox, review, polyphenols

Introduction

The flavonoids are a diverse group of polyphenolic compounds widely distributed in the plant kingdom and over 4000 structurally unique flavonoids have been identified in plant sources. These are primarily recognized as the pigments responsible for the many shades of yellow, orange, and red in of flowers, fruit, and leaves. These natural products were known for their beneficial effects on health long before they were isolated as the effective compounds. Research on flavonoids increased after the observation of French paradox i.e. the low cardiovascular mortality rate observed in Mediterranean populations in association with red wine consumption and a high saturated fat intake. The flavonoids in red wine are responsible, at least in part, for this effect. The other active ingredient in red wine responsible for this effect is resveratrol. Furthermore, studies suggest a protective role of dietary flavonoids against coronary heart disease and also indicate that flavonoid intake is inversely correlated with mortality due to coronary heart disease [[1], [2]]. There are numerous other positive effects associated with flavonoid intake and these will be discussed in following sections.

Major classes and Food sources of flavonoids

Flavonoids may be divided into six different major classes (flavonols, flavanones, flavones, isoflavones, flavonols and anthocyanidins) based on differences in molecular backbone structure[[3], [4]]. The major classes of flavonoids consist of

two fused six-membered rings (an aromatic A-ring and a heterocyclic C ring) connected through a carbon-carbon bridge to an aromatic B-ring. The specific C ring functional groups, unsaturation of C ring, and other details are given in Fig 1 and Table 1. The flavonol quercetin and the flavone apigenin are found in many fruits and vegetables, including onions, apples, broccoli, and berries. Naringenin is a citrus flavanone. Catechin and other catechins are abundant in green tea. Cyanidin and other anthocyanidins are largely responsible for the deep colors of berries, grapes, and red wine. Genistein is an isoflavone found predominantly in legumes. The flavonoid consumed most, in general, is quercetin, and the richest sources of flavonoids consumed in general are tea, onions, and apples [[1]]. However this is general information as both the amount and the source could vary appreciably in different countries.

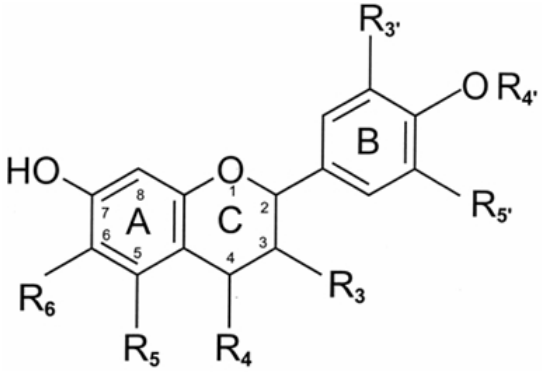

Figure 1: General structure and numbering pattern for common food flavonoids. See Table 1 for unique linkages, unsaturation positions and functional groups of each flavonoid subclass. For most food flavonoids, R_4, H, R_5 OH and R_6 H. Exceptions include glycitein, R_5 H, R_6 OH; and hesperitin, R_4, CH_3. Additional individual flavonoids within each subclass are characterized by unique functional groups at R_3, R_3', and R_5, [[4]].

Table 1: Flavonoid subclasses, their chemical characteristics, name of prominent food flavonoids and typical food sources [[4]] .

Flavonoid subclass	C ring unsaturation	C ring functional group	Prominent food flavonoids	Typical rich Food sources
Flavanol	none	3-hydroxy 3-O-gallate	(+)-Cathechin (+)-Gallocatechin (-)-Epicatechin-3-gallate	Teas, red grapes red wine, cocoa cocoa beverages and chocolate
Flavanones	none	4-Oxo	Eriodictyol Hesperetin Naringenin	Citrus foods like orange, lemon etc
Flavones	2-3 Double bond	4-Oxo	Apigenin Luteolin	Green leafy spices e.g. Parsley
Isoflavones	2-3 Double bond	4-Oxo	Daidzein Genistein Glycitein	Soybeans, soy foods and legumes
Flavonols	2-3 Double bond	3-Hydroxy, 4-Oxo	Isorhamnetin Kaempferol Myricetin Quercetin	Apple , tomato, cherry, Broccoli , yellow onion etc
Anthocyan-idins	1-2, 3-4 Double bonds	3-Hydroxy	Cyanidin Delphinidin Petunidin	Red, purple ,blue berries, Plum , strawberry etc

Note: position of B ring on C ring is 2 in all cases except Isoflavones where it is 3

Free radicals

Before we can understand the action of flavonoids and its impact on health we must first understand free radicals.

What are free radicals? [[5]]

Free radicals are molecules, usually of oxygen, that have lost an electron. That loss makes them unstable and reactive. They begin to covet their neighboring molecules' electrons. In stealing an electron, they operate as terrorists in the body. The most dangerous free radicals are the small, mobile, and highly reactive oxy radicals. Other dangerous atomic and molecular varieties of oxygen are known as reactive oxygen species (ROS). The mechanisms and the sequence of events by which free radicals interfere with cellular functions are not fully understood, but one of the most important events seems to be lipid peroxidation, which results in cellular membrane damage. This cellular damage causes a shift in the net charge of the cell, changing the osmotic pressure, leading to swelling and eventually cell death. Diseases like inflammation, coronary heart disease, cancer, diabetes, cystic fibrosis, rheumatoid arthritis, Alzheimer's disease, Parkinson's disease and many

more are now linked to oxy radicals and ROS [5] .The onslaught of free radicals and ROS also contributes to many of the less serious but still troubling symptoms of aging, such as wrinkled skin, gray hair, balding, and bodily stiffness.

Are all free radicals harmful?

Useful free radicals are created by our immune system to neutralize bacteria and viruses. This use of reactive oxygen species is remarkably effective in protecting the body against infectious organisms.

How are free radicals formed? [6]

Energy production: The energy-producing process in every cell generates oxy radicals and ROS as toxic waste, continuously and abundantly. Oxygen is used to burn glucose molecules that act as the body's fuel. In this energy-freeing operation, oxy radicals are thrown off as destructive by-products.

Stress: The stress response races the body's energy-creating apparatus, increasing the number of free radicals as a toxic by-product. Moreover, the hormones that mediate the stress reaction in the body, cortisol and catecholamines, themselves degenerate into free radicals. In effect, stressful life mass-produces free radicals.

External factors: Processed foods frequently contain high levels of lipid peroxides, which produce free radicals that damage the cardiovascular system. Cigarette smoke generates high free-radical concentrations; much of the lung damage associated with smoking is caused by free radicals. Air pollution has similar effects. Alcohol is a potent generator of free radicals (although red wine contains antioxidants that counteract this effect). In addition, free radicals can result from all types of electromagnetic radiation, including sunlight. Exposure to sunlight generates free radicals that age the skin, causing roughness and wrinkles. If the exposure is prolonged, skin cancer may result.

Antioxidants

These are substances that inhibit oxidation and guard the body from the damaging effects of free radicals. The natural defense mechanisms of the body include enzymes such as superoxide dismutase, catalase, and glutathione peroxidase and also nonenzymatic counterparts such as glutathione, vitamin C, and vitamin E. Due to the stressful life we lead today, the body's antioxidants are not enough to neutralize all free radicals produced. Thus we need to take foods which are rich in antioxidants [6].

Actions of flavonoids

The capacity of flavonoids to act as antioxidants and their role in the prevention of coronary heart diseases are the most important actions of flavonoids. The other actions are those against ulcers, viruses, inflammation, arthritis, osteoporosis and diarrhea.

Flavonoids as antioxidants

The best described and most useful property of almost every group of flavonoids is their capacity to act as antioxidants. The flavones and catechins seem to be the most powerful flavonoids for protecting the body against reactive oxygen species (ROS). Flavonoids can prevent injury caused by free radicals in various ways. One way is the direct scavenging of free radicals. Flavonoids are oxidized by radicals, resulting in a more stable, less-reactive radical, according to the following reaction [13].

$$FOH + R' \rightarrow FO' + RH$$

Where FOH is flavonoid and R' is free radical and FO' is less reactive free radical.

In other words, flavonoids stabilize the ROS by reacting with the reactive compound of the radical. Because of the high reactivity of the hydroxyl group of the flavonoids, radicals are made inactive. Epicatechin and rutin are also powerful radical scavengers [7].

Anti atherosclerotic effects

Atherosclerosis is a condition that results from the gradual build-up of fatty substances, including cholesterol, on the walls of the arteries. This build-up, called plaque, reduces the blood flow to the heart, brain and other tissues and can progress to cause a heart attack or stroke. This process is commonly referred to as hardening of the arteries. An elevated plasma low density lipoprotein (LDL) concentration is a primary risk factor for the development of atherosclerosis and coronary artery disease. Reactive oxygen species generated through lipid peroxidation can oxidatively modify i.e. oxidize the amino acid residues of LDL and this can initiate the atherosclerotic process .Flavonoids seems to suppress LDL oxidation and inflammatory progression in the artery wall. A Japanese study reported an inverse correlation between flavonoid intake and total plasma cholesterol concentrations, other clinical studies, as mentioned earlier, stated that flavonoid intakes protect against coronary heart disease [1, 8, 9].

Anti platelet aggregation and Anti thrombogenic effects

Platelet adhesion and subsequent aggregation contributes to both the development of atherosclerosis and acute platelet thrombus formation, followed by embolization of constricted arteries. The main anti aggregatory effect of flavonoids is thought to be by inhibition of thromboxane A_2 formation. In vitro studies showed that flavonoids bind to platelet membranes and may therefore have an accumulative effect over time. Thrombogenicity refers to the tendency of a material in contact with the blood to produce a thrombus (clot). Collagen is the most thrombogenic component of subendothelium, and flavonoids are known to inhibit the interaction of platelets on collagen coated surfaces [9, 10].

Anti ulcer effect

A peptic ulcer is an ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. Majority of peptic ulcers are associated with helicobacter pylori, a spiral-shaped bacterium that lives in the acidic environment of the stomach. Quercetin seems to play a very important role in the prevention and treatment of peptic ulcer. It acts by promoting mucus secretion, thereby serves as gastroprotective agent, also quercetin has been shown to inhibit the growth of helicobacter pylori bacterium in in-vitro studies [[9]] .Among other flavonoids, methyl-3-(+)-catechin interferes with the formation of histamine in gastric mucosa and hence produces the protective effect [[10]] .

Anti viral effects

Flavonoids of many types have antiviral effects in humans. First Cutting and his co workers described the antiviral effect of quercetin against rabies virus [[10]].Quercetin was later found to show inhibiting effects against herpes simplex virus. All the other flavonoids except rutin [[10]] too show anti viral effects against herpes simplex virus, respiratory syncytial virus, parainfluenza virus, and adenovirus[[7]]. Another fact which was observed was that when quercetin was added to cultures of several viruses associated with human maladies, viruses with an envelope were inhibited while those lacking such an envelope (like polio virus) were moderately or completely resistant to flavonoids [[3]] .

Anti inflammatory effects

Cyclooxygenase (COX) is an enzyme that plays an important role as inflammatory mediator and is involved in the release of arachidonic acid, which is a precursor for biosynthesis of eicosanoids like prostaglandins and prostacyclin. The release of arachidonic acid can be considered starting point for a general inflammatory response. Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain and this is the mechanism of action of well known class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs) examples include aspirin and ibuprofen. Select flavonoids like quercetin are shown to inhibit the cyclooxygenase pathway. This inhibition reduces the release of arachidonic acid. The exact mechanism by which flavonoids inhibit this enzyme is not clear. Another anti inflammatory property of flavonoids is their suggested ability to inhibit neutrophil degranulation. This is a direct way to diminish the release of arachidonic acid by neutrophils and other immune cells [[7] , [9]] .

Anti Arthritis effects

There are reports that people with rheumatoid arthritis experienced an improvement in their symptoms, when they switched from a typical western diet to a vegan diet with lots of uncooked berries, fruits, vegetables, which contains, apart from other nutrients, a lot of flavonoids [[12]] .

Anti osteoporotic effects

In an English study, bone mineral density was compared between older women who consumed tea and those who did not. Women in the study who drank tea had higher bone mineral density measurements than did those who did not drink tea. The flavonoids in tea might be responsible for the prevention of osteoporosis [[7]] .

Antidiarrheal effects

Cocoa beans have historically been used as a treatment for diarrhea. The exact mechanism of action and active ingredient was not known but the recent research attributes the antidiarrheal effect to the flavonoids present in cocoa [[11]].

Conclusions

Many large clinical studies conducted in last two decades have shown that flavonoids exert positive influence on health and diet rich in flavonoids alleviates and prevents many serious diseases. Flavonoids as antioxidants are ideal nutraceuticals for neutralizing stress induced free radicals. Many other actions of flavonoids like in cancer prevention have been reported in recent literature, but still large clinical trials are necessary until these effects are proved thoroughly. Flavonoids constitute a large part of U.S. nutraceuticals market and the current U.S. nutraceutical market was estimated at $28 billion in 2006 and the demand is expected to grow in coming years [[14]]. When Hippocrates, father of medicine, said that “Let food be thy medicine, and let thy medicine be food” he was probably referring to foods like flavonoids.

Acknowledgments

I would sincerely like to thank Dr. (Mrs.) S.S. Sathaye, Reader in Pharmacy, Institute of chemical technology for her support, suggestions, and encouragement throughout the production of this paper.

About the Author

My name is Jay M. Patel and I am a student of S.Y. B.tech (pharmaceutical and fine chemicals) at institute of chemical technology, University of Mumbai. My immediate career goals are to pursue post graduate and doctoral degrees in pharmaceutical sciences and gain experience as a scientist. I want to do research in pharmacognosy and in drug discovery from natural products, also I believe that in Ayurveda there is a rich treasure of knowledge and these should be exploited fully to find potential therapeutic agents which can prevent as well as treat lifestyle diseases like coronary heart diseases, diabetes mellitus type 2 etc which are increasingly taking epidemic proportions globally. My ambition is that after gaining sufficient experience in the research I want to eventually become an entrepreneur and start a pharmaceutical company which can some day become largest and most successful enterprise and help fulfill my vision of a world where everyone has the access to quality and affordable healthcare.

Endnotes

1. Hertog MG, Feskens EJ, Hollman PC, et al, 'Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study', *Lancet*, **342** (1993) 1007-1011.

2. Peluso MR, 'Flavonoids Attenuate Cardiovascular Disease, Inhibit Phosphodiesterase, and Modulate Lipid Homeostasis

in Adipose Tissue and Liver', *Exp Biol Med*, **231** (2006) 1287-1299.

3. Harborne JB, Mabry TJ, Mabry H, *The Flavonoids*, London, Chapman and Hall, 1974.

4. Beecher GR, 'Overview of Dietary Flavonoids: Nomenclature, Occurrence and Intake', *J Nutr*, **133** (2003) 3248-3254.

5. Halliwell B, 'Free radicals, antioxidants, and human disease: curiosity cause or consequence', *Lancet*, **344** (1994) 721-724.

6. Sharma H, Clark C, *Contemporary Ayurveda*, Edinburgh, Churchill Livingstone, 1998.

7. Nijveldt RJ, Nood E, Hoorn D, et al, 'Flavonoids: a review of probable mechanisms of action and potential applications', *Am J Clin Nutr*, **74** (2001) 418-425.

8. Hertog MG, Kromhout D, Aravanis C, et al, 'Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study', *Arch Intern Med*, **155** (1995) 381-386.

9. Middleton E, Kandaswami C, Theoharides TC, 'The Effects of Plant Flavonoids on Mammalian Cells: Implications for Inflammation, Heart Disease, and Cancer', *Pharmacol Rev*, **52** (2000) 673-751.

10. Farkas L, Gabor M ,Wagner H, et al, *Flavonoids and Bioflavonoids*, Amsterdam, Elsevier,1981.

11. Schuier M, Sies H, Illek B, et al, 'Cocoa-Related Flavonoids Inhibit CFTR-Mediated Chloride Transport across T84 Human Colon Epithelia', *J Nutr*, **135** (2005) 2320-2325.

12. Hanninen, Kaartinen K, Rauma AL, et al, 'Antioxidants in vegan diet and rheumatic disorders ', *Toxicology*, **155** (2000) 45-53.

13. Pietta PG, 'Flavonoids as Antioxidants', *J Nat. Prod*, **63** (2000) 1035-1042

14. Agricultural utilization research institute. [www.auri.org/news/ainjan03/08pag ...] (accessed Dec 2007)

Lethbridge Undergraduate Research Journal
ISSN 1718-8482