

# Some Therapeutic Effects of Flavonoids: Antispasmodic, Antihepatotoxic, Vasoprotective Effects

Nazire ÖZKAL\*, Erendiz ATASÚ\*, Rahmiye ERTAN\*\*, Gülgün AYHAN\*\*

## *Some Therapeutic Effects of Flavonoids:*

### *Antispasmodic, Antihepatotoxic, Vasoprotective Effects*

**Summary:** In this paper, flavonoid containing plants and pharmaceutical forms of natural and synthetically active flavonoid principals utilized today for providing antispasmodic, antihepatotoxic, and capillary resistance increasing effects are reviewed.

**Key words:** Flavonoid, antispasmodic, antihepatotoxic, vasoprotective

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## *Flavonoitlerin Bazı Terapötik Etkileri:*

### *Antispazmotik, Antihepatotoksik, Vazoprotektif Etki*

**Özet:** Bu çalışmada bugün, antispazmotik, antihepatotoksik ve kapiller rezistansı artırıcı amaçla kullanılan, flavonoit taşıyan bitkiler ile doğal ve sentetik flavonoit bileşiklerini taşıyan preparatlar derlenerek verilmiştir.

**Anahtar kelimeler :** Flavonoit, antispazmotik, antihepatotoksik, vazoprotektif

## INTRODUCTION

Flavonoids, due to their widespread occurrence in nature, are accepted as one of those phytochemical groups existing in everyday life, as a part of the dietary system, and a constituents of traditional folk drugs.

There are so many plant species used in traditional Turkish folk medicine<sup>1</sup>, some of which are utilized for therapeutic effects induced by flavonoids.

Flavonoids are derivatives of 2-phenylchromone or 2-phenylbenzo- $\gamma$ -pyrone which create flavone ring. Up to now nearly 2000 bioflavonoids and about 40 kinds of pharmacological and physiologic effects attributed to them have been defined<sup>2</sup>.

Among these effects, fungistatic, estrogenic, antibacterial, antiviral, spermicide, antihelminthic, diuret-

ic, reduction of tumor, activation of enzyme, protection of Langerhans islands, acceleration in respiration, antioxidant of vitamin C, reduction of iodine in thyroid, antinephrotoxic, various effects on cardiovascular system, antihistaminic and spasmolytic effects could be given as examples<sup>3-22</sup>.

Flavonoids can be grouped according to ring substituent patterns and the degree of benzopyron ring saturation such as shown Figure 1, flavanons, flavones, isoflavones, anthocyanins, chalcones and aurones; each of which has several families of hydroxy, methoxy and glycosylated derivatives<sup>23</sup>.

Today, naturally occurring flavonoids, as well as those synthesized, are used in modern medication for various therapeutic effects and among which, antispasmodic, coronary vasodilator, antihepatotoxic and capillary resistance increasing activities have the leading role<sup>24-26</sup>.

\* Department of Pharmacognosy, Faculty of Pharmacy, Ankara University, 06100 Tandoğan - ANKARA, TURKEY.

\*\* Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, 06100 Tandoğan-ANKARA, TURKEY.

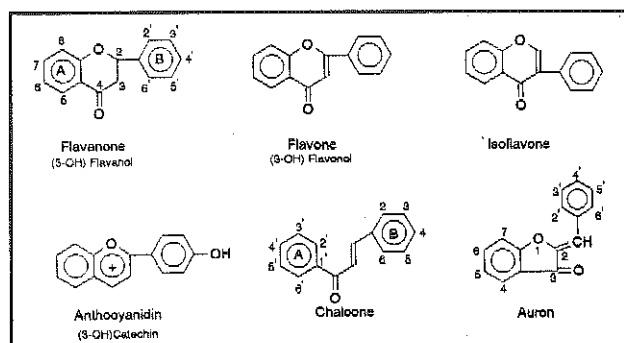


Figure 1. Flavonoid ring classifications

Researches for developing new synthetic flavonoids as curing agents, are continuing in various centers 25-33.

In our work, a survey of flavonoid containing plants and their active flavonoid contents as well as their pharmaceutical preparations used today, for their antispasmodic, antihepatotoxic and vasoprotective activities is presented.

### ANTISPASMODICS

Flavones and flavonols especially those with methoxy substituents are known as effective antispasmodics in smooth muscles. This activity may be related to their antiallergic effects that occur by inhibiting the secretion of allergic mediators responsible for muscle contractions from mast cells. It may also be due to the suppression of the contractility of smooth myocytes, by an antagonism of  $Ca^{++}$  uptake<sup>2</sup>.

Apigenin (5,7,4'-trihydroxyflavone), luteolin (5, 7, 3', 4'-tetrahydroxyflavone) and their methylated derivatives such as acacetin (apigenin-4'-methylether), diosmetin (luteolin-4'-methylether); and other methylated derivatives like artemetin (5-hydroxy- 3, 6, 7, 3', 4'-pentamethoxyflavone) and circineol (5, 4'-dihydroxy, 6, 7, 3'-trimethoxyflavone) are among the antispasmodic flavonoids; and plants such as parsley, mint, thyme etc. (Table 1), containing especially these constituents have been used in folk medicine for the same purpose.

Synthetic flavonoids, such as efloxate<sup>25</sup>, flavoxate (24) which are esters of the flavone ring are effective inhibitors of contractions of smooth muscles of cor-

onary and urinary system respectively (Table 2). Terflavoxate HCl is also an antispasmodic compound of which clinical experiments are being done<sup>32,34</sup>.

Table 1. Flavonoid Containing Plants with Antispasmodic Activity<sup>1,35</sup>

Species	Parts utilized	Other groups responsible for activity	Flavonoid Content
<b>ASCLEPIADACEAE</b>			
<i>Solanostemma argel</i> (Del) Hayne(36)	Leaves, stems		Kaempferol Kaempferol monoglycosides Kaempferol diglycosides
<b>COMPOSITAE</b>			
<i>Artemisia absinthium</i> L.	Flowers, herbs		Artemetin
<i>A.monosperma</i> Deille (37)	Aerial parts		7-O-methyleriodictyol
<i>Helichrysum</i> sp. (38-40)	Flowers, leaves		Kaempferol Methoxyflavonols Naringenin and their glycosides Bractein (auron glycoside) Isosalipurposide (chalcone glycoside)
<b>LAMIACEAE</b>			
<i>Mentha piperita</i> L.	Leaves	Volatile terpens	Apigenin-7-glucoside-4'-trans caffeate Apigenin-7-rutinoside-4'-trans caffeate
<i>Mentha spicata</i> L.	Leaves	Volatile terpens	Diosmetin-7-glucoside
<i>Thymus</i> sp. (41)	Aerial parts	Volatile phenolics	Apigenin Circineol, Luteolin Luteolin-7-glucoside
<b>LEGUMINOSAE</b>			
<i>Glycyrrhiza glabra</i> L. (42)	Roots	Triterpenoids	Liquiritigenin Isoliquiritigenin Glabramin Methoxykaempferol Formononetin and their glycosides
<i>Pscidia erythrina</i> L.(43)	Cortex		Isoflavonoids Piscidone Monoprenylated isoflavone Diprenylatedisoflavone
<b>PORTULACEAE</b>			
<i>Portulaca pilosa</i> L.(44)	Aqueous extract		Flavonoids
<b>UMBELLIFERAE</b>			
<i>Petroselinum crispum</i> (Millar) A.W. Hill	Aerial parts, roots, seeds		Apigenin Luteolin Chrysoeriol Quercetin and their glycosides

### ANTIHEPATOTOXICS

The usage of the plant extracts against jaundice and other pathologic conditions of the liver exist in many traditional modes of therapy. Flavonoid containing

species of Compositae (Table 3) and *Silybum marianum* L. among them, which is one of the oldest plants cultivated, have always been prominent. *S. marianum* contains apigenin and its glycosides along with the flavonolignans, namely silybin, silydianin, silychristin known as the silymarin group (Table 4).

The antihepatotoxic activity of flavonoids and in particular, of the silymarin group depends on the inhibition of lipoxygenase by the constituents mentioned above (Figure 2).

Table 2. Antispasmodic Flavonoids and Their Preparations Used in Today's Therapy<sup>45,46</sup>

SYNTHETICAL	
<b>Eflorate (7-flavone ethylhydroxyacetate) :</b>	
Dilatan® (Italy)	
Recordil® (Belgium, France, Italy, Switzerland)	
<b>Flavoxate (3-methylflavon-8-carboxylic acid - β - piperidinoethyl ester) :</b>	
Bradalone® (Japan)	
Genurin® (Italy)	
Spasuret® (Germany)	
Urispas® (Switzerland, Turkey, UK, USA, etc.)	
Urispadol® (Denmark, Norway)	

Table 3. Flavonoid Containing Plants with Anti-hepatotoxic Activity<sup>53</sup>

Species	Parts utilized	Other groups responsible for activity	Flavonoid Content
<b>BURSERACEAE</b>			
<i>Canarium manil</i> King (54)	Nux-shell		Biflavonoid Agathisflavon
<b>COMPOSITAE</b>			
<i>Baccharis</i> sp. (55,56)	Epigeous parts	Cynarin	Hisbutilen Cynaroside (Luteolin-7-glucoside)
<i>Cynara scolymus</i> L. (57)	Leaves		Scolymoside (Luteolin-7-rhamnosyl-glycoside) (Luteolin-7-rutinoside - 4'-glycoside)
<i>Eupatorium cannabinum</i> L. (58)	Flowers, leaves	Caffeic acid Chlorogenic acid	Quercetin Rutin Hyperoside
<i>Silybum marianum</i> L. (59-62)	Flowers, leaves		Apigenin and glycosides Silybin Silydianin Silychristin
<b>GUTTIFERAE</b>			
<i>Garcinia kola</i> Heckel (63)	Seeds	Xanthones Benzophenones Lactones	Biflavanones Kolaviron
<b>LEGUMINOSAE</b>			
<i>Buteo monosperma</i> (Lam.) O. Kuntze (56)	Flowers		Isobutrin Butrin

The inhibition of lipoxygenase protects the unsaturated fatty acids of the liver cell membranes from oxidation and thus from lysis<sup>47</sup>.

New researches have proved that flavonolignans also help the formation of liver RNA, DNA and proteins, thus supporting the regeneration of the liver tissue<sup>48</sup>.

There are also evidence that γ-pyrone is the structure responsible for the antihepatotoxic activity<sup>49-52</sup>.

Table 4. Antihepatotoxic Flavonoids and Their Preparations Used in Today's Therapy<sup>45,46</sup>

NATURAL	
<b>Silimarin Group (Silibin, Silidianin, Silicrytin) :</b>	
Cardomarin® (Spain)	
Dura Silymarin® (Germany)	
Eparsil® (Italy)	
Legalon® (Belgium, France, Germany, Italy, Spain, etc.)	
Silimarina® (Spain)	
Silirex® (Italy)	
Siliver® (Italy)	

**VASOPROTECTIVES**

The vasoprotective effects of flavonoids have been discussed since Szent Gyrcy's assertions<sup>2,35</sup>. It has now been proved that rutin and its methoxylated derivatives; naringenin, hesperidin and diosmin reduce hemorrhage and vascular purpura, extend Vit C effect and reverse cerebral oedema<sup>35</sup> (Table 5-6).

**CONCLUSION**

Flavonoids, as a drug, raised high hopes in the 50's; and then faced failure as a consequence of insufficient scientific support.

Due to new developments in molecular pharmacology and biochemistry, the biological effects of flavonoids are again gaining prominence, as the biochemical basis of various activities of flavonoids becomes lucid. This basis is, in fact, rather simple, in spite of the various biochemical stages involved; and is being more and more clearly conceived, as the en-

Membrane Phospholipide

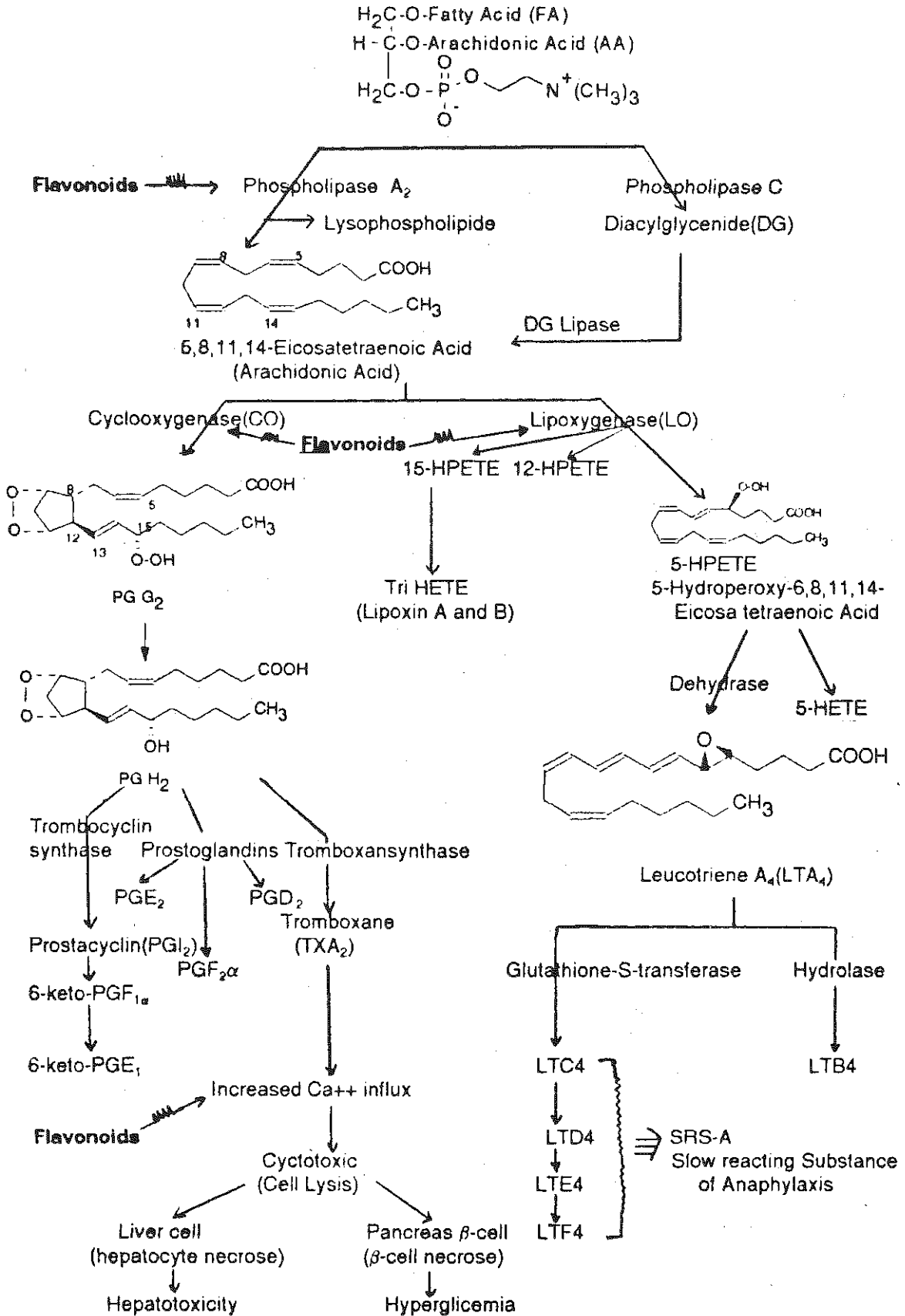


Figure 2. Inhibition Exerted by Flavonoids on Arachidonic acid Cascade<sup>64</sup>

zymatic aspects of the autocoids originated from membrane phospholipids are being solved.

**Table 5. Flavonoid Containing Plants with Vasoprotective Activity<sup>1, 35</sup>**

Species	Parts utilized	Other groups responsible for activity	Flavonoid Content
<b>CAPRIFOLIACEAE</b>			
<i>Sambucus</i> sp.	Flowers	Tannins	Quercetin Kaemferol
<b>COMPOSITAE</b>			
<i>Achillea</i> sp. (41)	Herb	Azulenes	Patuletin
<b>CUPRESSACEAE</b>			
<i>Cupressus sempervirens</i> L.		Tannins	Bioflavonoids
<b>GUTTIFERAE</b>			
<i>Garcinia mannii</i> (63)	Bark		Maniflavanone
<b>HIPPOCASTANACEAE</b>			
<i>Aesculus hippocastanum</i> L.	Cortex	Tannins	Kaemferol Quercetin and their glycosides Methoxyflavonols
<b>JUGLANDACEAE</b>			
<i>Juglans regia</i> L.	Leaves	Tannins	Kaemferol Quercetin and their glycosides Methoxyflavanones
<b>SALICACEAE</b>			
<i>Populus nigra</i> L.	Buds		Chrysin Galangin Rhamnetin-2,5-dihydroxy- 7-methoxyflavanone
<b>SCROPHULARIACEAE</b>			
<i>Verbascum</i> sp.	Flowers, leaves		Luteolol and derivative

**Table 6. Vasoprotective Flavonoids and Their Preparations Used in Today's Therapy<sup>45,46</sup>**

NATURAL	SEMISYNTHETIC
Bioflavonoids (Citrus sp. flavonoid comp. = Flavanones):	Troxerutin (Trioxethyl rutin)
Flavovenly®	Paroven® (Australia, England)
Diosmin® (Methoxy luteolin glycoside):	Posorutin® (Germany)
Daflon® (France, Italy, Spain, Turkey)	Relvene® (France)
Diosmil® (France)	Fulvene® (France)
Flebosmil® (France)	Rutilemone® (France)
Flebosten® (Italy)	Vareoid® (Australia, England)
Insuven® (Spain)	Veno SL® (Germany)
Tovene® (Germany)	Venoruton® (Belgium, Germany, Italy, Netherland, Turkey)

Allergen imposed capillary permeability and oedema formation are reversed by flavonoid mixtures of especially combinations of diosmin and hesperidin<sup>65</sup>. Free oxygen radicals are abundantly generated in wounded tissues, thus leading to capillary fragility which is related to arachidonic acid cascade, as indicated above. Flavonoids inhibit this pathway and exert beneficial effects on allergy in general, on hepatotoxicity, hyperglycemia and diabetes related vascular disorders<sup>66,67</sup>.

Mixtures of 90% diosmin and 10% hesperidin inhibit<sup>65</sup> phosphodiesterase in the collateral networks of vascular tissues and prolong the vasoactivity of noradrenaline, in a manner connected to their interaction with free oxygen radicals; and thus are placed, together with semisynthetic rutin derivatives, among the vasoprotective agents of today's European medication.

Synthetical flavone derivatives and naturally occurring silymarin group are important curing agents in spasms of smooth muscle and pathologies of liver, respectively.

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