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- Note -

Screening of Flavonoid Compounds with HMG-CoA Reductase Inhibitory Activities

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3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely used drugs for lowering blood lipid levels and preventing cardiovascular diseases. HMG-CoA reductase is a key enzyme to control the biosynthesis of cholesterol. We have tested HMG-CoA reductase-inhibitory activity on the flavonoids of 98 species in vitro. The anti-hypercholesterolemic activities of flavonoids were studied using an HMG-CoA reductase assay equipped with a 96-well UV plate. This assay was based on the spectrophotometric measurement of the decrease in absorbance, which represents the oxidation of NADPH by the catalytic subunit of HMG-CoA reductase in the presence of the substrate HMG-CoA. Among the clinically available statins, pravastatin was used as a positive control. Among the tested compounds, kuraridin, morin and sophoraflavanone G showed strong inhibition activities. In particular, morin and sophoraflavanone G inhibited HMG-CoA reductase by 45.0% and 54.6% at a concentration of 10 μg/ml, and the IC_{50} values were calculated to 13.31 μg/ml and 7.26 μg/ml respectively.

Key words : HMG-CoA reductase, kuraridin, morin, sophoraflavanone G

서 론

심혈관계 질환은 2013년 통계 자료에 따르면 세계적으로 질환별 사망률 순위에 있어서 1위이며 우리나라에서도 사망률 2위인 질병이다[82]. 심혈관계 질환으로 인한 사망자 수가 2013년에는 전 세계적으로 1,700만 명에 이르며 우리나라에서도 57,182 명으로 알려져 있다[82]. 여러 역학 조사 결과로부터 심혈관계 질환 발생의 주 위험 요인이 고콜레스테롤혈증, 혈압, 흡연 그리고 운동 부족으로 알려지면서[2, 25, 26], 식생활을 비롯한 생활 습관의 변화와 함께 약물 요법을 병행하여 혈청 콜레스테롤 수치를 낮추고자 중재하는 노력들이 시행되었고, 그 결과 이들 질환의 발병률도 감소하는 것으로 나타났다[7].

체내에서 사용되는 콜레스테롤의 70% 이상은 체내 콜레스테롤 신생합성 과정에서 만들어지므로, 콜레스테롤 합성을 저해하는 것이 혈장 콜레스테롤을 감소시키는 효과적인 방법이다. 현재 임상적으로 고콜레스테롤혈증 치료에 가장 널리 처방되고 있는 statin [3, 27]은 콜레스테롤 생합성 과정의 율속효소인 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase의 경쟁적 저해제이다[21]. Statin에 의해 콜레스테롤 생합성이 저해되면 세포 내 콜레스테롤 농도가 감소하고, 이에 대해 세포는 sterol regulating binding protein-2 (SREBP-2)의 활성화와 LDL-receptor 수의 증가를 통해 혈액 콜레스테롤의 세포 내 유입을 증가시키게 되고 이로 인해 혈중 콜레스테롤 농도는 낮아지게 된다[109]. 현재 사용되고 있는 statin으로는atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin 등이 있다. Statin의 효과적인 혈장 콜레스테롤 저하 작용으로 인한 심혈관 질환 위험성 감소 효과에도 불구하고 당뇨병 발병 위험성의 증가, 간 손상, 신경계 이상 및 근육통 등의 부작용들이 보고되면서 statin의 안전성이 또한 중요한 이슈가 되고 있으며, pravastatin은 다른 statin에 비해 당뇨병 발생 위험성과 부작용 발생률이 낮은 것으로 알려져 있다[73]. 따라서 statin의 단독 사용으로 인한 부작용은 감소시키면서 치료 효과는 상승시킬 수 있는 치료제 또는 치료보조제의 개발을 위한 연구가 계속되고 있다.

식이 플라보노이드는 phenylchoromane 또는 flavone ring을 가지고 있는 식물성 색소 그룹이다[86]. 고콜레스테롤혈증과 심혈관계 질환에 대한 플라보노이드의 효과가 많은 연구에서 입증되었다. 일본 여성을 대상으로 한 횡단적 연구에서 플라보노이드 섭취의 증가가 혈장 총 콜레스테롤과 LDL 농도를 감소시킨 것으로 나타났다[4]. 그리고 isoflavone 섭취가 혈장

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LDL 콜레스테롤 및 중성 지방 농도와 역 상관 관계를 나타낸다는 메타 분석 결과도 있다[1, 32, 116].

전보에서 저자 등은 천연물로부터 HMG-CoA reductase 저해제를 탐색하고자 선행 연구에서 분리한 70여종의 phenol성 물질에 대해서 HMG-CoA reductase 저해 활성을 측정하여 1,4-Naphthoquinone 및 plumbagin의 고콜레스테롤혈증 예방 및 치료제의 가능성을 제시한 바 있다[106]. 따라서 본 연구에서는 전보에 이은 후속 연구로서 다양한 약용 및 자생식물로부터 혈장 콜레스테롤 감소 활성을 가지는 물질을 발굴하고자 식물체로부터 분리한 flavonoid compound 및 관련 화합물 98종에 대해 HMG-CoA reductase 저해 활성을 *in vitro*에서 탐색하였으며, 그 결과를 보고하는 바이다.

재료 및 방법

실험재료

본 실험에서 사용한 98종의 플라보노이드 화합물은 Table 1에 나타내었다. 97종의 화합물은 이전의 선행연구에서 참고문헌에 제시된 방법으로 천연물로부터 분리 및 구조 동정하였고, flavonol (3-hydroxyflavone)은 Simga사(St. Louis, MO, USA)에서 구입하여 사용하였다. 시료는 Dimethyl sulfoxide (DMSO)로 1 mg/ml 농도로 희석하여 최종 농도 10 μg/ml에서 활성을 측정하였다.

HMG-CoA reductase 활성

콜레스테롤 합성 저해 활성은 HMG-CoA reductase assay kit (Sigma, St. Louis, MO, USA)를 사용하여 *in vitro*에서 측정하였다. 간략하면, HMG-CoA reductase에 의해 HMG-CoA가 mevalonate로 환원될 때 NADPH가 $NADP^+$ 로 산화되는 정도를 340 nm에서 15분간 흡광도의 변화로 측정하였다(Molecular Devices Co., Sunnyvale, CA, USA). Pravastatin을 positive control로 사용하여 시료의 저해 활성과 비교하였다. HMG-CoA reductase 활성 저해율(%)은 아래의 계산식과 같이blank의 흡광도 변화(100% 활성)에 대한 시료의 흡광도 변화로 계산하였다.

활성 저해율(%) = (1 - 시료의 흡광도 변화/Blank의 흡광도 변화) ×100.

이후 HMG-CoA reductase 활성 저해율이 20% 이상인 시료들에 대해서는 50%의 활성 저해를 나타내는 시료 농도(IC_{50})를 구하였다.

결과 및 고찰

플라보노이드는 사실상 모든 식이성 식물에 존재하는 저분자의 폴리페놀 화합물이다[95]. 주로 꽃과 과일에서 노란색, 주황색, 빨간색을 띠며 가을 단풍의 색깔로도 알려져 있다. 식물체에는 구조적으로 독특한 4,000여 가지 이상의 플라보노이드가 있는 것으로 확인되었다. 이들 화합물은 phenyl benzopyrone 골격(C6-C3-C6)의 공통적인 구조를 가지고 있으며, 이중 결합과 중앙에 위치한 고리의 개방 여부에 따라 flavonols, flavanols, flavanonols, flavanones, flavones 및 isoflavones으로 분류된다[13, 20, 31, 79, 95].

플라보노이드는 래디칼 소거[77], 항산화[6], 항혈전[5, 85, 101], 항허혈증[93, 96, 108], 항부정맥[30], 항고혈압[23, 75], 항염증 활성[94], 산화성 스트레스에 의해 유도된 세포사멸 저해[87] 등을 통해 심혈관계 질환의 치료에 효과를 나타내는 것으로 알려져 있으며[80, 113], 실제 감귤류와 다양한 약용식물 유래의 플라보노이드는 전 세계적으로 전통 의학에 널리 사용되고 있다[14, 16, 39, 92, 99].

본 연구에서 플라보노이드 및 관련 화합물 98종의 HMG-CoA reductase 저해 활성을 측정한 결과(Fig. 1, Fig. 2, Fig. 3 및 Fig. 4), 시료 농도 10 μg/ml에서 저해율이 가장 높은 화합물은 sophoraflavanone G 로 54.6%의 저해를 보였고, 다음으로 morin 45.0%, kuraridin 21.9%의 순으로 나타났다. 한편 시료 농도 50 μg/ml에서 20% 이상의 저해 활성을 나타낸 시료로는, kenusanone A (37.0%), isoquercitrin (26.6%), liquiritigenin (25.8%), kurarinone (24.4%), 7,8-dihydroxyflavone (23.6%) 등이 있었다(data not shown). 이상의 시료들 가운데 10 μg/ml에서 저해 활성이 높게 나타난 3종의 플라보노이드 화합물을 대상으로 IC_{50}값을 계산하였다(Table 2). 그 결과, sophoraflavanone G의 IC_{50}는 7.3 μg/ml, morin과 kuraridin은 각각 13.3 μg/ml과 87.4 μg/ml으로 나타났다. Positive control로 사용한 pravastatin의 저해율은 0.1 μg/ml에서 92.9%였다.

Morin[2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one]은 무화과와 같은 뽕나무과 식물에서 주로 분리되지만 아몬드 껍질과 황목에서도 분리되는 황색 색소인 플라본이다. Morin은 강력한 항산화제[111, 112], xanthine oxidase 저해제[115], 세포 증식 저해제[64], apoptosis 유도제[78]로 작용하며 구강암 예방 활성을 나타내는 것으로 알려져 있다[56]. 또한 아라키돈산 대사에서 lipoxygenase와 cyclooxygenase 활성 조절제로 작용하여[66] 급성 대장염 쥐에서 장 염증 활성을 저해하며[24, 83], lipopolysaccharide로 유도된 패혈성 쇼크의 발병률을 감소시키는 것으로 알려져 있다[22].

한편 sophoraflavanone G는 *Sophora flavescens* Aiton (Leguminosae)의 건조 뿌리에서 분리된 주요 lavandulylated flavanones 중 하나로, 항 말라리아, 항균, 항 바이러스 및 항산화 작용이 있으며, lipopolysaccharide로 처리 한 RAW 세포에서 nitric oxide와 prostaglandin E2의 생성을 저해하는 것으로 알려져 있다[9, 18, 37, 63, 107]. *Sophora flavescens* 의 건조뿌리인 Sophorae radix는 전통적으로는 해열제, 진통제, 구충제 및 건위제로 사용되어 온 약초로서[34, 59, 65], formononetin, kushenol E, kushenol B, sophoraflavanone G, kushenol L,

Table 1. The list of 98 flavonoid compounds

No.	Compounds	References
1	amentoflavone	50
2	amurenoside B	44
3	anhydroicaritin 3-O-rhamnoside	54
4	apigenin	102
5	artemetin	49
6	astragalin (kaempferol 3-O-β-D-glucoside)	90
7	astrapterocarpan 3-O-glucoside (methylnissolin 3-O-β-glucoside)	69
8	avicularin (quercetin 3-O-α-L-arabinofuranoside)	42
9	baicalin	89
10	baicalein	33
11	bilobetin	50
12	calycosin	69
13	calycosin 7-O-glucoside	69
14	catharticin (alaternin, rhamnocitrin 3-O-rhamininoside)	71
15	(+)-catechin	60
16	chrysin	33
17	daidzein	69
18	7,8-dihydroxyflavone	117
19	diosmetin 7-O-glucoside	104
20	echinoisoflavanone	60
21	echinoisosophoranone	60
22	epicatechin acetate	19
23	epimedin A	43
24	epimedin B	43
25	epimedin C	43
26	epimedoside A	43
27	eupatilin	97
28	evodioside B	113
29	formononetin	69
30	formononetin acetate	69
31	galangin	52
32	galangin 3-O-methyl ether	52
33	genistein	87
34	genistin	57
35	flavonol (3-hydroxyflavone)	Sigma
36	hesperidin (hesperetin 7-O-rutinoside)	113
37	hyperin (hyperoside, quercetin 3-O-galactopyranoside)	62
38	icariin	54
39	isoginkgetin	50
40	isoliquiritigenin	101
41	isoliquiritigenin monoacetate	101
42	isomucronulatol 7-O-glucoside	69
43	isoquercitrin (quercetin 3-O-glucopyranoside)	68
44	isorhamnetin	46
45	isorhamnetin 3-O-galactoside (casticin)	55
46	isosophoranone	60
47	isospinosin	72
48	isoxanthohumol	51
49	kaemferide	52

Table 1. Continued

No.	Compounds	References
50	kaempferol	8
51	kaempferol 3-O-(6′′-coumaroyl-glucosyl)(1→2)rhamnoside	50
52	kaempferol 3-O-glucosyl(1→2)rhamnoside	50
53	kaempferol 3-O-2′′,6′′-dirhamnosylglucoside	50
54	kaempferol 3-O-4‴-acetylrhamininoside	71
55	kaempfero 3-O-rhamininoside	71
56	kenusanone A	60
57	kenusanone C	60
58	kuraridin	38
59	kurarinone	38
60	linarin	102
61	liquiritin	101
62	liquiritigenin	69
63	liquiritigenin acetate	69
64	luteolin	68
65	luteolin 7-O-glucoside (cynaroside)	102
66	morin	48
67	naringenin	28
68	naringin	41
69	neohesperidin	80
70	neohesperidin dihydrochalcone	109
71	nicotiflorin (kaempferol 3-O-rutinoside)	90
72	ochnaflavone	83
73	oroxylin A	67
74	phloretin	75
75	phlorizin	12
76	poncirin	29
77	puerarin	11
78	quercetin	45
79	quercetin 3-O-robinobioside	103
80	quercetin 3-O-(6′′-coumaroyl-glucosyl)(1→2)rhamnoside	50
81	quercetin 3-O-2′′,6′′-dirhamnosylglucoside	44
82	quercetin 3-O-2′′,6′′-dirhamnosylgalactoside	44
83	rhoifolin (apigenin 7-O-neohesperidoside)	68
84	robinin	53
85	rutin	90
86	sciadopitysin	50
87	silibinin (silybin)	70
88	sophoraflavanone G	51
89	sophoflavescenol	38
90	spinosin	10
91	6′′′′-feruloylspinosin	10
92	swertisin	73
93	swertisin acetate	73
94	tiliroside (kaempferol 3-O-(6"-p-coumaroylglucoside))	88
95	trifolirhizin	40
96	vitexicarpin	17
97	vitexin (apigenin 8-C-β-D-glucoside)	113
98	wogonin	35

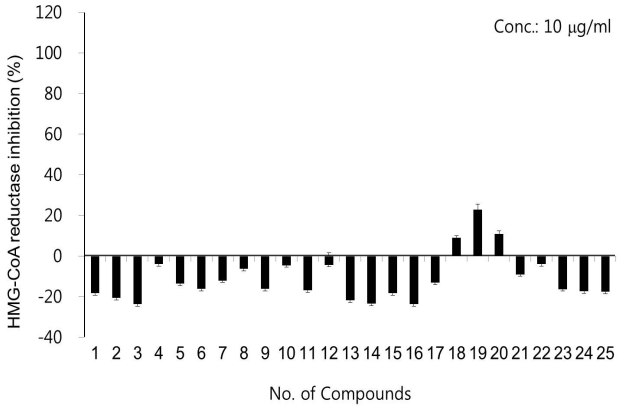

Fig. 1. HMG-CoA reductase inhibition (%) of flavonoid compounds (From No. 1 to 25). Final concentration of sample is 10 μg/ml. Compounds: 1, amentoflavone; 2, amurenoside B; 3, anhydroicaritin3-O-rhamnoside; 4, apigenin; 5, artemetin; 6, astragalin (kaempferol 3-O-β-D-glucoside); 7, astrapterocarpan 3-O-glucoside (methylnissolin 3-O-β-glucoside); 8, avicularin (quercetin 3-O-α-L-arabinofuranoside); 9, baicalin; 10, baicalein; 11, bilobetin; 12, calycosin; 13, calycosin 7-O-glucoside; 14, catharticin (alaternin, rhamnocitrin 3-O-rhamininoside); 15, (+)-catechin; 16, chrysin; 17, daidzein; 18, 7,8-dihydroxyflavone; 19, diosmetin 7-O-glucoside; 20, echinoisoflavanone; 21, echinoisosophoranone; 22, epicatechin acetate; 23, epimedin A; 24, epimedin B; 25, epimedin C.

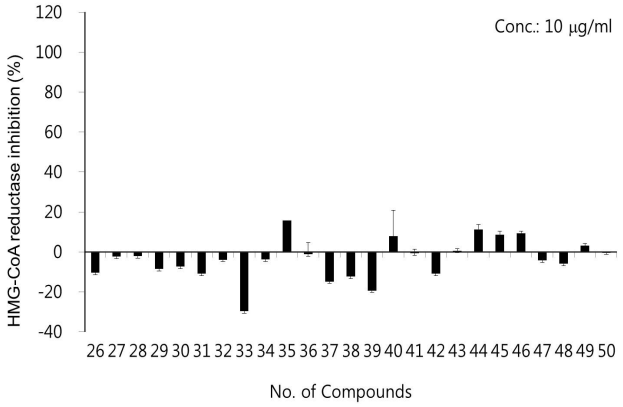

Fig. 2. HMG-CoA reductase inhibition of flavonoid compounds (From No. 26 to 50). Final concentration of sample is 10 μg/ml. Compounds: 26, epimedoside A; 27, eupatilin; 28, evodioside B; 29, formononetin; 30, formononetin acetate; 31, galangin; 32, galangin 3-O-methylether; 33, enistein; 34, genistin; 35, flavonol (3-hydroxyflavone); 36, hesperidin (hesperetin 7-O-rutinoside); 37, hyperin (hyperoside,quercetin 3-O-galactopyranoside); 38, icariin; 39, isoginkgetin; 40, isoliquiritigenin; 41, isoliquiritigenin monoacetate; 42, isomucronulatol 7-O-glucoside; 43, isoquercitrin (quercetin 3-O-glucopyranoside); 44, isorhamnetin; 45, casticin (isorhamnetin 3-O-galactoside); 46, isosophoranone; 47, isospinosin; 48, isoxanthohumol; 49, kaemferide; 50, kaempferol.

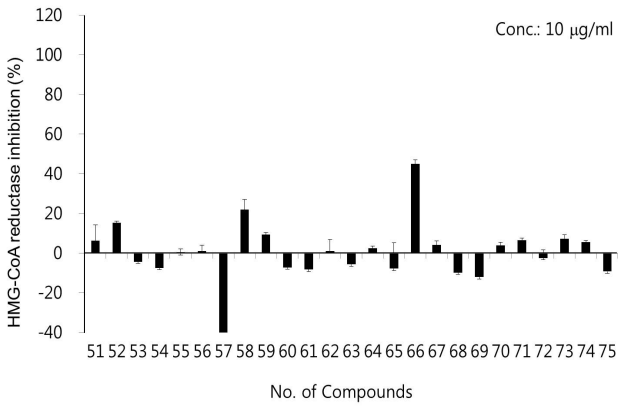

Fig. 3. HMG-CoA reductase inhibition (%) of flavonoid compounds (From No. 51 to 75). Final concentration of sample is 10 μg/ml. Compounds: 51, kaempferol 3-O-(6''-coumaroyl-glucosyl)(1→2)rhamnoside; 52, kaempferol 3-O-glucosyl(1→2)rhamnoside; 53, kaempferol 3-O-2'', 6''-dirhamnosylglucoside; 54, kaempferol 3-O-4'''-acetylrhamininoside; 55, kaempferol 3-O-rhamininoside; 56, kenusanone A; 57, kenusanone C; 58, kuraridin; 59, kurarinone; 60, linarin; 61, liquiritin; 62, liquiritigenin; 63, liquiritigenin acetate; 64, luteolin; 65, luteolin 7-O-glucoside(cynaroside); 66, morin; 67, naringenin; 68, naringin; 69, neohesperidin; 70, neohesperidin dihydrochalcone; 71, nicotiflorin(kaempferol 3-O-rutinoside); 72, ochnaflavone; 73, oroxylin A; 74, phloretin; 75, phlorizin.

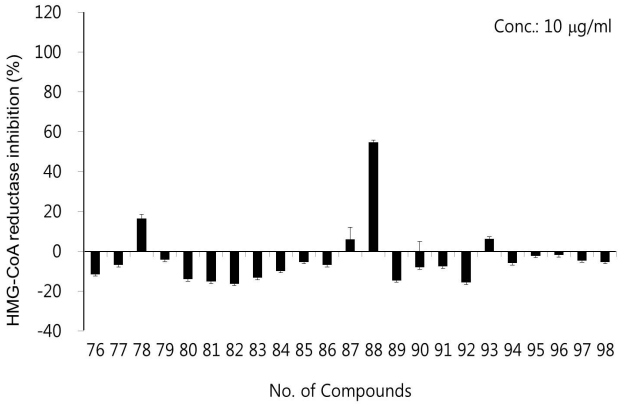

Fig. 4. HMG-CoA reductase inhibition (%) of flavonoid compounds (From No. 76 to 98). Final concentration of sample is 10 μg/ml. Compounds: 76, poncirin; 77, puerarin; 78, quercetin; 79, quercetin 3-O-robinobioside; 80, quercetin 3-O-(6''-coumaroyl-glucosyl)(1→2)rhamnoside; 81, quercetin 3-O-2'',6''-dirhamnosylglucoside; 82, quercetin 3-O-2'',6''-dirhamnosylgalactoside; 83, rhoifolin (apigenin 7-O-neohesperidoside); 84, robinin; 85, rutin; 86, sciadopitysin; 87, silibinin (silybin); 88, sophoraflavanone G; 89, sophoflavescenol; 90, spinosin; 91, 6'''-feruloylspinosin; 92, swertisin; 93, swertisin acetate; 94, tiliroside (kaempferol 3-O-(6"-p-coumaroylglucoside)); 95, trifolirhizin; 96, vitexicarpin; 97, vitexin (apigenin 8-C-β-D-glucoside); 98, wogonin.

Table 2. HMG-CoA reductase inhibition (%) and half maximal inhibitory concentration (IC_{50}) of flavonoid compounds

Compounds	Concentration (μg/ml)					
	0.1	10.0	25.0	50.0	100.0	IC_{50}
pravastatin	92.9					
kuraridin		21.9	ND	43.2	85.5	87.4
morin		45.0	62.3	73.3	ND*	13.3
sophoraflavanone G		54.6	77.5	117.6	ND	7.3

*ND : Not determined.

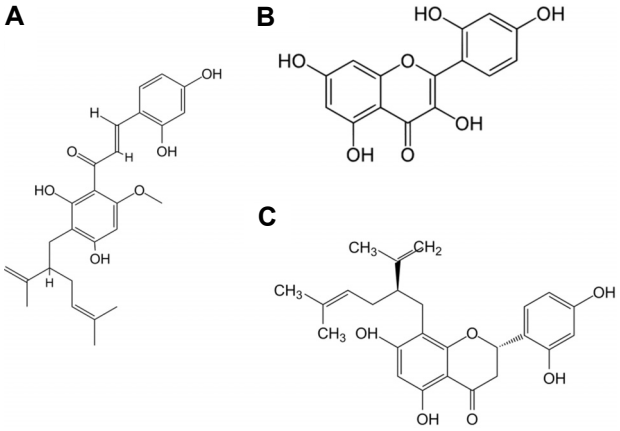

Fig. 5. Structure of finally selected flavonoidic compounds. A: kuraridin, B: morin, C: sophoraflavanone G.

kushenol M, kuraridin, kurarinone, kushenol N, 및 kushenol F와 같은 다양한 플라보노이드가 함유되어 있는 것으로 보고되어 있다[15, 36, 97, 100].

상기와 같이, 98종의 플라보노이드 화합물을 대상으로 HMG-CoA reductase 저해 활성을 탐색한 결과, sophoraflavanone G 와 morin의 저해 활성이 가장 강력한 것으로 확인되었으며, 이들을 이용한 고콜레스테롤혈증 개선 효과를 가지는 건강기능성 식품 또는 약품의 개발을 위한 추후 연구가 필요한 것으로 사료된다.

감사의 글

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초록 : 플라보노이드 화합물로부터 HMG-CoA reductase 저해 활성 물질 탐색

손건호[1] · 이주연[1] · 이정순[2] · 강삼식[3] · 손호용[1] · 권정숙[1]*
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심혈관계 질환은 질환별 사망률 순위에 있어서 세계에서는 1위이며, 우리나라에서는 2위인 질병이다. 심혈관계 질환 발생의 주 위험 요인인 콜레스테롤은 HMG-CoA reductase에 의해 간에서 신생합성이 조절된다. 현재 고콜레스테롤혈증 치료에 statin이 널리 사용되고 있지만 광범위한 부작용이 보고되고 있어서 이를 대체하거나 보조할 수 있는 천연물 유래의 기능성 물질 개발이 필요한 실정이다. 따라서 본 연구에서는 혈장 콜레스테롤 감소 활성을 가지는 물질을 발굴하고자 98종의 플라보노이드 및 그와 관련된 화합물들을 대상으로 10 μg/ml 농도에서 HMG-CoA reductase 저해 활성을 탐색하였다. 그 결과, sophoraflavanone G, morin, 및 kuraridin이 각각 54.6%, 45.04% 및 21.9%의 저해활성을 타내었으며, IC_{50}값을 계산한 결과, sophoraflavanone G가 7.3 μg/ml로 가장 낮았으며 morin과 kuraridin은 각각 13.3 μg/ml과 87.4 μg/ml으로 확인되어, 향후 고콜레스테롤혈증 예방 및 치료제의 가능성을 제시하였다.