

Effects of *Ficus carica* and Its Compounds on Smooth Muscle Contractility

Sadettin DEMIREL^{**}, Ipek Nazli SINAG^{**}

Effects of *Ficus carica* L. and Its Compounds on Smooth Muscle Contractility

SUMMARY

Ficus carica L., commonly known as fig, belongs to the genus *Ficus* L. in the Moraceae family. In traditional medicine, it is recommended to treat metabolic diseases and coughs. *F. carica* exhibits therapeutic effects on cancer, diabetes, inflammation, and tuberculosis, possibly thanks to its rich compositions of phytochemicals. Fig can reduce hypertension, alleviate muscle spasms, and relieve constipation. A total of 64 bioactive compounds were detected that affect smooth muscle contraction-relaxation. The compounds were classified as follows: flavonoids (16), terpenes (14), fatty acids (8), phenolic compounds (7), alcohols (5), coumarins (4), aldehydes (3), esters (2), organic acids (2), phenylpropanoids (2), and phytosterol (1). The study provides a comprehensive literature search on *F. carica* components influencing smooth muscle contractility. *F. carica* may be used to treat smooth muscle dysfunction-related disorders, including asthma, hypertension, and gastrointestinal dysmotility.

Keywords: *Ficus carica* L., phytochemical compound, smooth muscle, contractility.

Ficus carica L. ve Bileşenlerinin Düz Kas Kontraktilitesi Üzerindeki Etkileri

ÖZ

İncir olarak da bilinen *Ficus carica* L. Moraceae familyasından *Ficus* L. cinsine aittir. Geleneksel tıpta metabolik hastalıkların ve öksürüğün tedavisi için önerilmektedir. *F. carica*, muhtemelen zengin fitokimyasal kompozisyonlarından dolayı kanser, diyabet, inflamasyon ve tüberküloz üzerinde terapötik etkiler göstermektedir. İncir hipertansiyonu azaltabilir, kas spazmlarını hafifletebilir ve konstipasyonu giderebilir. Düz kas kasılma-gevşemesini etkileyen toplam 64 biyoaktif bileşen belirlenmiştir. Bu bileşikler aşağıda sınıflandırılmıştır: flavonoidler (16), terpenler (14), yağ asitleri (8), fenolik bileşikler (7), alkoller (5), kumarinler (4), aldehitler (3), esterler (2), organik asitler (2), fenilpropanoidler (2) ve fitosterol (1). Bu çalışma, düz kas kontraktilitesini etkileyen *F. carica* bileşenleri üzerine kapsamlı bir literatür taraması sunmaktadır. *F. carica* astım, hipertansiyon ve gastrointestinal dismotilite dahil olmak üzere düz kas disfonksiyonu ile ilişkili hastalıkların tedavisinde kullanılabilir.

Anahtar Kelimeler: *Ficus carica* L., fitokimyasal bileşen, düz kas, kontraktilite.

Received: 26.03.2026

Revised: 21.07.2026

Accepted: 25.07.2026

^{*} ORCID: 0000-0002-3629-5344, Department of Physiology, Faculty of Medicine, Bursa Uludag University, Bursa, Türkiye

^{**} ORCID: 0009-0008-8810-9276, Department of Physiology, Faculty of Medicine, Bursa Uludag University, Bursa, Türkiye

INTRODUCTION

Traditionally, medicinal plants are used to treat cardiovascular diseases due to vasorelaxant and anti-diabetic effects (Demirel, 2024). *Ficus carica* L., usually termed as fig, is a species of the Moraceae family. The *Ficus* L. genus includes about 800 species around the world (Rahmani & Aldebasi, 2017). This plant is deciduous, having a height of approximately 3-10 m, with numerous branches and multi-lobed leaves. It is among the first cultivated plants and was also mentioned in the Quran and Bible. Fig has been a sign of fruitfulness, power, wisdom, and sexuality since ancient times (Özatalay, 2014). The main producers of figs are in the Mediterranean region, particularly Türkiye, Spain, Greece, Morocco, and Egypt (Garibaldi, Schulte, Nabaes Jodar, Gomez Carella, & Kremen, 2021). It is important for human health and can be consumed in various forms, such as fresh and dried (Rasool et al., 2023). They are rich in phenolic compounds, fibers, and polyunsaturated fatty acids, but the dried fruit of figs contains higher sugar levels and calories than fresh fruits (Barolo, Ruiz Mostacero, & López, 2014). Ethnopharmacological studies have shown that the different parts obtained from the fig tree, such as fruit, leaf, root, and latex, have antispasmodic, antitussive, anticolic, laxative, and diuretic properties (Mawa, Husain, & Jantan, 2013).

Traditional uses of *Ficus carica* L.

Ayurvedic, Siddha, and Unani traditional medicine systems have highlighted the therapeutic potential of figs (Badgujar, Patel, Bandivdekar, & Mahajan, 2014). In folk medicine, *F. carica* has been used to treat cardiovascular, metabolic, respiratory, and inflammatory diseases (Patil, Bhangale, & Patil, 2010). Fig root is recommended for use in ringworm and leucoderma treatment. Fig leaves are used to treat helminth, nutritional anemia, cough, and irritant potential (Mohamad et al., 2011; Saeed & Sabir, 2002). Fig latex is believed to cure warts (Martínez, 2008). The fruit of the fig is used as an anti-constipation and expectorant (Khadabadi, Gond, Ghiware, & Shendarkar, 2007).

Biological properties of *Ficus carica* L.

Experimental studies reported that *F. carica* has antioxidant, antiepileptic, anti-neurodegenerative, anti-convulsant, antiarthritic, antiplatelet, antiangiogenesis, antimutagenic, anti-inflammatory, anti-HIV, antibacterial, antifungal, antipyretic, and aphrodisiac properties (Bouyahya, Ben Said, Bakri, & Dakka, 2016; Fazel et al., 2024; Hajam & H, 2022). Aysin, Simsek Ozek, Acet, and Koc (2024) showed that two higher concentrations of fig latex (1/36 and 1/12) cause a significant decrease in A549 cell viability. A study conducted on rifampicin-induced rats demonstrated that treatment with the petroleum ether extract of *F. carica* leaves reduces alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels from 88 U/L to 66 U/L and from 289 U/L to 184 U/L, respectively (Gond & Khadabadi, 2008). A study indicated that water and methanolic extracts from fig leaves dramatically inhibit α -glucosidase and α -amylase. Both extracts showed higher α -glucosidase and α -amylase activity than acarbose (57.56% and 58.4%, respectively) (Ergul, Ergul, Eruygur, Atas, & Ucar, 2019). The pulp of fig fruit causes an improvement in fasting lipid profile, atherogenic index of plasma (AIP), and low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio while enhancing HDL (Perveen et al., 2021). The MIC value of the 80% methanolic extract of the *F. carica* leaf against *Mycobacterium tuberculosis* H37Rv was 1600 μ g/mL (Khadabadi et al., 2007). Gilani, Mehmood, Janbaz, Khan, and Saeed (2008) demonstrated that the ripe dried fruit of fig relaxes spontaneous and low K^+ (25 mM)-evoked contractions of jejunal smooth muscle. However, its activity is abolished by glibenclamide, a ATP-sensitive potassium (K_{ATP}) channel blocker. A study reported that the hexane-soluble fraction of fig leaves at 10 μ g/mL reduces the number of TRAP-positive multinucleated cells in bone marrow-derived macrophages by $96.4 \pm 0.7\%$ (Park et al., 2009). 70% methanol extract from *F. carica* decreases myocardial infarction size to 72.2% at a concentration of 1 mg/mL compared with the control (Allahyari, Delazar, & Najafi, 2014).

Phytochemical compounds of *Ficus carica* L.

Phytochemical research on the different parts of *F. carica* has identified many bioactive compounds using various analysis techniques (Table 1.). In the *n*-butanol extract of *F. carica* leaves, 27 compounds were revealed: quercetin-3-*O*-rutinoside, fumaric acid, hyperoside, and chlorogenic acid as the domain compounds (Renda, Barut, Ceren, & Aydin, 2023). 4-methylhepta-1,4-diene, anisole, and 2,3-dimethylpent-1-ene were the major compounds of the water extract of fig leaves, whereas 2H-furo[2,3-*H*]-1-benzopyran-2-one, bergapten, and methyl linolenate were the major compounds of the methanolic extract (Ergul et al., 2019). The volatile aroma composition of fig fruit categorized five classes as follows: alcohols (3-methyl-1-butanol, 2-methyl-1-butanol, 1-hexanol, 2-ethyl hexanol, benzyl alcohol, phenylethyl alcohol, and 1-dodecanol), esters (ethyl isobutyrate, ethyl butyrate, (E)-2-butenic acid ethyl ester, ethyl 2-methylbutyrate, ethyl isovalerate, ethyl tiglate, ethyl hexanoate, cis-3-hexenyl acetate, hexyl acetate, trans-2-ethyl hexanoate, and propanoic acid, 2-methyl-, 1-(1,1-dimethylethyl)-2-methyl-1,3-propanediyl ester), hydrocarbons (*p*-xylene), terpenes (α -pinene, *p*-cymene, limonene, linalool, and E-caryophyllene), and aldehydes (benzaldehyde and nonanal) (Kiralan & Kiralan, 2023). The most abundant constituents are furfural, 5-methyl-2-furaldehyde, and benzeneacetaldehyde in the volatile oil obtained from *F. carica* fruit (Li et al., 2012). Fig pulp includes numerous volatile aromatic compounds, such as β -caryophyllene; (E)-2-hexanal; 5-(hydroxymethyl)furfural; 2,6-di-*tert*-butyl-4-methylphenol; benzaldehyde; germacrene D; furfural; phthalic acid, diisobutyl ester; limonene; β -cubebene; β -selinene; α -humulene; (+)-sativene; α -curcumene; β -bisabolene; β -sesquiphellandrene; β -(methylamino) ethanol; *n*-nonanoic acid; acetic acid; 2,3-dihydro-3,5-dihydroxy-6-methyl-4-pyrone; dihydroxyacetone, and dihydro-4-hydroxy-2(3H)-furanone (Gozlekci, Kafkas, & Ercisli, 2011). The main constituents analyzed in the lyophilized extract of

fig pulp were malic acid, citric acid, and shikimic acid (Oliveira et al., 2009). In fig peel, many flavonoids and phenolic acids were detected, including quercetin-3-*O*-rutinoside, cyanidin-3-*O*-rutinoside, and 5-*O*-caffeoylquinic acid (Calani et al., 2022). β -caryophyllene, germacrene D, and 2,6-di-*tert*-butyl-4-methylphenol were determined as the predominant compounds of fig peel (Gozlekci et al., 2011). A metabolomic study on the female flowers of fig presented that phenethyl caffeate, apigenin, and isoacteoside are the primary components (Wang, Song, Wang, Chen, & Ma, 2021). Fatty acids like γ -linolenic acid, linoleic acid, and oleic acid are abundant in the *F. carica* seed oil, as discovered by GC-FID (gas chromatography-flame ionization detector) analysis (Tas, 2019). A study determined nine compounds in the sterol composition of fig seed oil (Ustun-Argon, Sari, Gokyer, & Buyukhelvacigil-Ozturk, 2021). In the chloroform fraction from fig latex, lupeol acetate and lupeol palmitate were isolated, while β -sitosterol and lupeol were found in the unsaponifiable fraction (Jeivad et al., 2020; Oliveira et al., 2010). *F. carica* hairy root is rich in phenolic acids, such as chlorogenic acid, gallic acid, rosmarinic acid, and coumaric acid (Amani, Mohebodini, Khademvatan, Jafari, & Kumar, 2021, 2024). In the different parts of fig, umbelliferone, cyanidin-3-*O*-glucoside, β -amyrin, α -linolenic acid, cis-5,8,11,14,17-eicosapentaenoic acid, palmitic acid, palmitoleic acid, ferulic acid, quercetin-3-*O*-glucoside, oleanolic acid, heptanol, methyl butanoate, methyl salicylate, menthol, α -cubenene, copaene, β -elemene, aromadendrene, α -caryophyllene, cinnamic aldehyde, cinnamic alcohol, eugenol, angelicin, β -pinene, eucalyptol, stearic acid, xanthotoxin, prunetin, pinocembrin, morin, kumatakenin, luteolin, acacetin, velutin, luteolin 7-*O*-glucoside, apigenin 7-*O*-glucoside, tangeretin, nobiletin, and cinnamic acid were detected (Barolo et al., 2014; Gibernau, Busser, Frey, & Hossaert-McKey, 1997; Innocenti, Bettero, & Caporale, 1982; Mawa et al., 2013; Oliveira et al., 2009; Rahmani & Aldebasi, 2017; Saeed & Sabir, 2002; Tarlacı, 2021; Tas, 2019; Wang et al., 2021).

Table 1. Major compounds identified from different parts of *Ficus carica* L.

Parts	Analysis techniques	Extracts/Fractions	Classes	Major compounds	References
Leaf	LC-HRMS	<i>n</i> -butanol	Flavonoid	Quercetin-3- <i>O</i> -rutinoside Hyperoside	(Renda et al., 2023)
			Organic acid	Fumaric acid	
			Phenolic compound	Chlorogenic acid	
Fruit	GC-MS	Volatile oil	Aldehyde	Furfural 5-Methyl-2-furaldehyde Benzeneacetaldehyde	(Li et al., 2012)
Pulp	HS/GC-MS	Volatile aroma	Terpene	β -Caryophyllene	(Gozlekci et al., 2011)
			Aldehyde	(<i>E</i>)-2-Hexanal 5-(Hydroxymethyl)furfural	
Peel	HS/GC-MS	Volatile aroma	Terpene	β -Caryophyllene Germacrene D	(Gozlekci et al., 2011)
			Phenolic compound	2,6-Di- <i>tert</i> -butyl-4-methylphenol	
Flower	Metabolome		Phenylpropanoid	Isoacteoside	(Wang et al., 2021)
			Flavonoid	Apigenin	
Seed	GC-FID	Seed oil	atty acid	γ -Linolenic acid Linoleic acid Oleic acid	(Tas, 2019)
Latex	GC-ITMS/ HPLC-DAD	Unsaponifiable fraction	Phytosterol	β -Sitosterol Lupeol	(Oliveira et al., 2010)
Hairy root	HPLC	-	Phenolic compound	Chlorogenic acid Gallic acid Coumaric acid	(Amani et al., 2021)

Effects of *Ficus carica* L. on smooth muscle contractility

This section describes the effects of *F. carica* on smooth muscle contractility. The following studies show that *F. carica* exhibits antihypertensive, anti-constipation, and antispasmodic properties.

Hypotensive and antihypertensive activity

The aqueous methanol extract obtained from the fruit of *F. carica* (1000 mg/kg) significantly reduced heart rate and systolic, mean, and diastolic blood pressure in normotensive and glucose-induced hypertensive rats. The extract significantly attenuated heart rate and force of contraction at 0.000001-10 μ g/mL doses in a concentration-dependent manner. However, 0.01 mg/mL of *F. carica* extract did not elicit significant blockage in heart rate and force of contraction stim-

ulated with epinephrine (10^{-5} M) or CaCl_2 (10^{-5} M). These results suggested that the aqueous methanol extract of *F. carica* has hypotensive and antihypertensive activities (Alamgeer, Iman, Asif, & Saleem, 2017).

Activity on constipation

F. carica paste decreased colon transit time while ameliorating stool type and abdominal discomfort. The supplementation may reduce pain related to functional constipation (Baek et al., 2016). Similarly, administration of *F. carica* paste alleviated chronic constipation in the loperamide-treated animals. In this regard, *F. carica* paste improved thickness and mucin areas in the distal colon, fecal pellet number, and water content, as well as peristalsis and tension of the intestinal ileum (Lee et al., 2012).

Antispasmodic activity

The aqueous extract of ripe dried fruit of *F. carica* (0.1-3.0 mg/mL), containing alkaloids, coumarins, flavonoids, saponins, and terpenes, led to a relaxation in isolated rabbit jejunum contracted with low K^+ (25 mM) concentration. The spasmolytic activity is associated with K_{ATP} channel activation (Gilani et al., 2008).

Alcohols

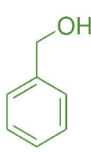
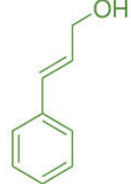
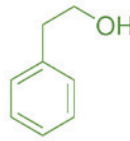
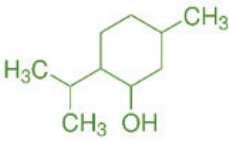
				
Benzyl alcohol	Cinnamic alcohol	Phenylethyl alcohol	Heptanol	Menthol

Figure 1. Alcohols of *Ficus carica* L. involved in smooth muscle contractility

Benzyl alcohol

Benzyl alcohol did not lead to a significant change in the contraction induced by ACh (acetylcholine) and antigen in tracheal smooth muscle (Abraham, Abraham, & Ahmed, 1996). In the bronchi, it could alleviate contractions induced by histamine, serotonin, and electrical field stimulation (EFS). Benzyl alcohol elicited relaxation in bronchi contracted by ACh. This effect was not blocked by propranolol, indomethacin, ouabain, or removal of the epithelium. The aromatic alcohol elevated cyclic adenosine monophosphate (cAMP) levels in bronchial rings treated with ACh. Benzyl alcohol inhibited PIP_2 hydrolysis in ACh-mediated contractions. Thus, the inhibitory effect of benzyl alcohol was associated with PIP_2 turnover (Tamaoki et al., 1990).

Cinnamic alcohol

Psidium guajava L. essential oil includes cinnamic alcohol from its main compounds, which led to attenuation in jejunal smooth muscle contractility (Rashed, Khan, Wahid, Khan, & Shah, 2016). Cinnamic alcohol could relax phenylephrine (PE)-evoked con-

Effects of phytochemical compounds of *Ficus carica* L. on smooth muscle contractility

This section presents 64 phytochemical compounds from various parts of *F. carica* involved in smooth muscle contractility. The phytochemical compounds have been categorized into 11 classes as follows: flavonoids (16), terpenes (14), fatty acids (8), phenolic compounds (7), alcohols (5), coumarins (4), aldehydes (3), esters (2), organic acids (2), phenylpropanoids (2), and phytosterol (1) (Figures 1-11.).

tractions in the aorta with endothelium. This vasorelaxation was decreased by N omega-Nitro-L-arginine methyl ester (L-NAME), MB, ODQ, glibenclamide, and 4-AP. The alcohol exhibited suppressor effects on contraction induced by calpeptin, a Rho-kinase activator (Kang, Yang, Morgan, & Shin, 2012).

Phenylethyl alcohol

Phenylethyl alcohol obtained from *Rosa damascena* Mill. caused inhibition in PE-induced aorta and U46619-induced mesenteric artery contractions. The vasorelaxant effects of phenylethyl alcohol were likely dependent on opening BK_{Ca} channels (Singh et al., 2023).

Heptanol

Heptanol, a gap junction uncoupler, inhibited neurogenic and myogenic contractions in the vas deferens smooth muscle (Venkateswarlu, Dange, & Manchanda, 1999).

Menthol

Menthol slightly triggered relaxation in the methacholine-contracted trachea. It attenuated EFS-mediated

ed spike contraction, likely due to parasympathetic activation (Wang, Liu, Chao, & Lee, 2016). The cyclic alcohol inhibited colon circular smooth muscle constricted with EFS and carbachol (CCh). Menthol concentration-dependently caused a decrease in the amplitude of spontaneous phasic contractions but did not affect the frequency and the basal tonus. This effect was altered by nifedipine, an L-type voltage-dependent calcium channel (VDCC) blocker (Amato,

Liotta, & Mulè, 2014). Incubation with menthol abolished CaCl_2 -evoked contractile responses in the coronary artery, comparable to nifedipine. 1 mM menthol treatment produced relaxant responses on KCl-contracted endothelium-intact and -denuded aorta, coronary, and mesenteric arteries (Cheang et al., 2013). Menthol had a suppressor action on detrusor smooth muscle contractions stimulated by CCh (Nomoto et al., 2008).

Aldehydes

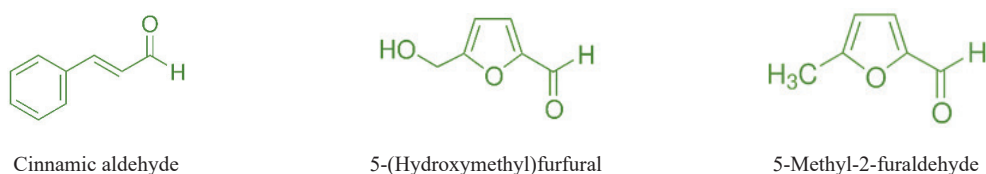


Figure 2. Aldehydes of *Ficus carica* L. involved in smooth muscle contractility

Cinnamic aldehyde

Cinnamic aldehyde potentiated contraction in the basal tone of the ileum. Atropine, tetrodotoxin (Na^+ channel blocker), PPADS (purinergic receptor antagonist), and A967079 (TRPA1 channel antagonist) alleviated the contractile responses. This compound produced relaxation of histamine-induced contractions, which were inhibited by TEA. Cinnamic aldehyde had contrary effects on detrusor smooth muscle. Capsaicin desensitization abolished relaxation evoked by cinnamic aldehyde (Sandor, Bencsik, Dekany, & Bartho, 2019). Cinnamic aldehyde elicited endotheli-

um-independent relaxation in contracted aortic segments with KCl (Alvarez-Collazo et al., 2014).

5-(Hydroxymethyl)furfural

5-(Hydroxymethyl)furfural induced uterine contractions via cholinergic receptors (Sewram, Raynor, Mulholland, & Raidoo, 2001).

5-Methyl-2-furaldehyde

5-Methyl-2-furaldehyde abolished aortic and prostatic smooth muscle contractions induced by PE (Martišienė, Zigmantaitė, Pudžiuvėlytė, Bernatoniėnė, & Jurevičius, 2023).

Coumarins

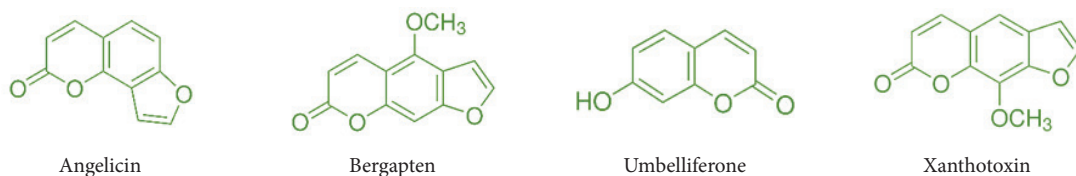


Figure 3. Coumarins of *Ficus carica* L. involved in smooth muscle contractility

Angelicin

Angelicin presented a relaxant effect on PE-elicited contractions of aortic segments, which may be associated with the inhibition of TRPC3 channels (Kasahun Gebremeskel et al., 2017).

Bergapten

Bergapten suppressed spontaneous and K^+ -induced contractions as a Ca^{2+} channel blocker in the jejunum (Aslam et al., 2022). The furanocoumarin exerted myorelaxation activity on the jejunal smooth

muscle in the concentration range of 0.0001-1 μ M. Furthermore, higher concentrations of bergapten produced dual contractile/relaxant effects (Skalicka-Woźniak, Mendel, Chłopecka, & Dziekan, 2016).

Umbelliferone

In dysmenorrhea uterine smooth muscle, umbelliferone mitigated Ca^{2+} , ET-1, and PGE_2 levels and suppressed the expression of P2X3. However, it augmented nitric oxide (NO) levels (Liu et al., 2023). Umbelliferone vasodilated mesenteric arteries, inhib-

ited plasmalemmal and sarcolemmal Ca^{2+} channels, and opened K^+ channels (Jesus et al., 2022).

Xanthotoxin

PE-contracted corpus cavernosum was relaxed by xanthotoxin (Chiou, Huang, Chen, & Chen, 2001). The coumarin exerted an inhibitory effect on pulmonary artery rings contracted with NE (norepinephrine). The vasorelaxation was endothelium-independent (Wang, Zhang, & Kang, 1997).

Esters



Figure 4. Esters of *Ficus carica* L. involved in smooth muscle contractility

Methyl butanoate

Methyl butanoate is one of the major components of essential oil extracted from *P. guajava* fruit. The essential oil blunted aortas contracted by high K^+ and PE. Furthermore, the essential oil showed inhibitory effects on spontaneous and high K^+ -mediated jejunum contractions, similar to verapamil, a Ca^{2+} channel blocker. But further studies are needed to elucidate the effects of methyl butanoate, one of the major constituents of the essential oil, on the smooth muscles (Rasheed et al., 2016).

Methyl salicylate

Topical administration of methyl salicylate led to an increase of short-term vasorelaxation in the skin. However, the administration may not promote blood flow to the striated muscle (Versteeg et al., 2024). A cream containing 15% methyl salicylate and 10% menthol also had vasorelaxant activity (Dolen et al., 2015).

Fatty acids

<chem>CCCCCCCCC=CCCCCCCCCCCCCCCC(=O)O</chem>	<chem>CCCCCCCCC=CCCCCCCC=CCCCCCCCCCCCCCCC(=O)O</chem>	<chem>CCCCCCCCC=CCCCCCCC=CCCCCCCCCCCCCCCC(=O)O</chem>
α -Linolenic acid	cis-5,8,11,14,17-Eicosapentaenoic acid	γ -Linolenic acid
<chem>CCCCCCCCC=CCCCCCCC=CCCCCCCCCCCCCCCC(=O)O</chem>	<chem>CCCCCCCCC=CCCCCCCCCCCCCCCCCCCCCCCC(=O)O</chem>	<chem>CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC(=O)O</chem>
Linoleic acid	Oleic acid	Palmitic acid
<chem>CCCCCCCCC=CCCCCCCCCCCCCCCCCCCCCCCC(=O)O</chem>	<chem>CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC(=O)O</chem>	
Palmitoleic acid	Stearic acid	

Figure 5. Fatty acids of *Ficus carica* L. involved in smooth muscle contractility

Alpha-linolenic acid

Flaxseed oil, rich in α -linolenic acid, led to an increase of epinephrine-induced contractile responses through reactive oxygen species (ROS) and thromboxane A_2 (TXA₂) (Nunes et al., 2014). In high-fat diet-fed streptozotocin rats, the omega-3 fatty acid supplementation avoided endothelial dysfunction via increasing endothelial nitric oxide synthase (eNOS) activity while decreasing oxidative/nitrative stress via inhibiting ONOO⁻ production, iNOS, and NADPH oxidase expression (Zhang et al., 2013). α -Linolenic acid caused a decrease in systolic blood pressure mediated by prostacyclin (PGI₂) and NO through bradykinin activation in spontaneously hypertensive rats (SHRs) (Sekine, Sasanuki, Aoyama, & Takeuchi, 2007).

cis-5,8,11,14,17-Eicosapentaenoic acid

cis-5,8,11,14,17-Eicosapentaenoic acid, docosahexaenoic acid, and sesamin combination had an excitatory effect on eNOS activity in human umbilical vein endothelial cells (eNOS), resulting in augmented NO levels. The excitatory effect was elicited as follows: Ca²⁺ signaling by sesamin or membrane lipid alterations by these omega-3 fatty acids (Morita et al., 2023). Abnormal contractions in inflammatory bowel diseases were suppressed by cis-5,8,11,14,17-eicosapentaenoic acid. The inhibitory activity was exhibited on ileal and colonic longitudinal smooth muscle through voltage-dependent Ca²⁺ channels (Obara et al., 2021). It produced relaxation responses on U46619-contracted saphenous veins via K⁺ channels (Daci et al., 2020). Acute incubation with cis-5,8,11,14,17-eicosapentaenoic acid reduced relaxant responses to KCl by inhibiting Na⁺/K⁺ ATPase activity in the pulmonary artery. Chronic incubation with cis-5,8,11,14,17-eicosapentaenoic acid caused a decrease in KCl-induced relaxation by downregulating protein expression of the sodium pump $\alpha 1$ isoform (Singh, Garg, & Mishra, 2012). In the pulmonary artery, the fatty acid promoted endothelium-dependent vasorelaxation through NO release. Meanwhile, it induced endothelium-in-

dependent vasorelaxation, possibly inhibiting L-type Ca²⁺ channels and serotonin-mediated contraction (Singh, Kathirvel, Choudhury, Garg, & Mishra, 2010). cis-5,8,11,14,17-Eicosapentaenoic acid improved the imbalance between endothelium-derived relaxant and constrictor factors by inhibiting cyclooxygenase-2 (COX-2) expression and the ERK/NF- κ B signaling pathway (Matsumoto, Nakayama, Ishida, Kobayashi, & Kamata, 2009). It evoked endothelium-derived relaxing factor (EDRF) release, which may be related to a decrease in the intimal thickness of autogenous vein graft (Komori et al., 1995). cis-5,8,11,14,17-Eicosapentaenoic acid caused repression of the trachea contracted by leukotriene C4 and D4. cis-5,8,11,14,17-Eicosapentaenoic acid-mediated relaxation was mediated via the 5-lipoxygenase pathway (Isogai, Taki, Suzuki, Takagi, & Satake, 1991).

Gamma-linolenic acid

Evening primrose oil, rich in γ -linolenic acid, attenuated ACh-mediated relaxation responses in the isolated aorta, corpus cavernosum, and mesenteric vascular bed of diabetic rats (Jack, Keegan, Cotter, & Cameron, 2002). Treatment with the α -lipoic acid and γ -linolenic acid combination showed synergistic interactions on corpus cavernosum smooth muscle from streptozotocin-induced diabetic rats; the administration ameliorated NO-mediated neurogenic- and endothelium-dependent relaxation (Keegan, Cotter, & Cameron, 2001). Histamine and methacholine, both of which are contractile agents, led to a decrement in the relaxing effect of γ -linolenic acid in both epithelium-intact and -denuded trachea; however, the reduction was greater after the removal of epithelium (Kahler & Du Plooy, 1998). In the uterus, it improved the spontaneous decrease of inotropic constancy. The omega-6 fatty acid was converted into PGE1, a potent relaxant factor (Chaud, Franchi, Gimeno, & Gimeno, 1988).

Linoleic acid

In porcine aortic endothelial cells, linoleic acid attenuated EDRF production, such as NO and PGI₂, and

decreased endothelial Ca^{2+} responses by increasing cAMP levels through suppressing cAMP-hydrolyzing phosphodiesterase (Wei, Takeuchi, & Watanabe, 2013). It inhibited the effect of bradykinin on NO and PGI_2 release in ECs (Satoh, 2013). Oxidized linoleic acid upregulated eNOS mRNA levels in bovine aortic ECs (Ramasamy, Parthasarathy, & Harrison, 1998). This polyunsaturated fatty acid caused membrane hyperpolarization via Na^+/K^+ -ATPase pump activation, resulting in porcine coronary VSMC relaxation (Pomposiello, Alva, Wilde, & Carretero, 1998).

Oleic acid

Oleic acid treatment downregulated COX-2 mRNA expression. Similarly, it reduced ET-1 released by human umbilical vein ECs (Bass, Soukup, Ghio, & Madden, 2020). Oleic acid partially exerted its inhibitory effect on the aorta relaxed by ACh, but the effect was insignificant (Bass et al., 2019). It deteriorated endothelial function: increase of ROS and abolishment of insulin receptor-mediated eNOS stimulation (Gremmels et al., 2015). The omega-9 fatty acid inhibited Kir6.1 mRNA and protein expression in human umbilical artery smooth muscle cells (SMCs). It also exhibited inhibitory activity on K_{ATP} current. However, the activity of oleic acid was attenuated by NO donor DETA-NO except protein kinase C (PKC) inhibitor GFX. Thus, oleic acid may contract VSMCs via the PKC signaling pathway (Bai et al., 2013). The oleic acid diet improved endothelium-mediated relaxation compared to the linoleic acid diet in type 2 diabetes patients (Ryan et al., 2000). In bovine pulmonary artery ECs, oleic acid blocked eNOS activity by a PKC-independent mechanism. The MUFA reduced ACh-induced relaxant responses by inhibiting eNOS activity in the rabbit femoral artery (Davda et al., 1995). The vascular activity of oleic acid is partially similar to that of oxidized LDL. In the rabbit aorta, oleic acid decreased cyclic guanosine monophosphate (cGMP) levels; however, it induced contraction medi-

ated by NE (Niu, Liu, Hu, & Chen, 1995).

Palmitic acid

$\text{K}_{\text{Ca}2.3}$ (small-conductance calcium-activated potassium channels)-mediated relaxation was impaired by palmitic acid incubation in mesenteric small arteries. It inhibited $\text{K}_{\text{Ca}2.3}$ current in human umbilical vein ECs. Palmitic acid induced the downregulation of $\text{K}_{\text{Ca}2.3}$ channel protein expression. The decreasing activity was abolished by Nox, p38-MAPK, or NF- κ B inhibitors. Thus, the saturated fatty acid may contribute to endothelial dysfunction through the Nox/ROS/p38-MAPK/NF- κ B pathway (Wang et al., 2019). Incubation with palmitic acid suppressed vasorelaxant factor NO production in human umbilical vein ECs (Moers & Schrezenmeir, 1997).

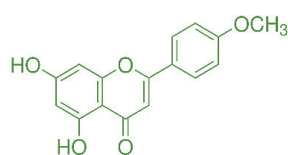
Palmitoleic acid

Gap junction uncoupler palmitoleic acid exhibited blockage activity on the vasomotion of mesenteric terminal arterioles by inhibiting remote Ca^{2+} responses (Braunstein et al., 2009). IP_3 diffusion from mesenteric SMCs to ECs is blocked by palmitoleic acid (Lambole et al., 2005). It did not influence bradykinin-induced relaxation in the ciliary artery with intact endothelium (Morf, Bény, Flammer, & Haefliger, 2002). In the mesenteric arterial bed, the omega-7 fatty acid could not inhibit the vasorelaxant effect of anandamide (Harris, McCulloch, Kendall, & Randall, 2002). Palmitoleic acid had no effect on endothelial hyperpolarization induced by bradykinin or substance P in coronary arteries (Bény & Schaad, 2000).

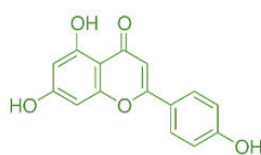
Stearic acid

In aortic segments, treatment with stearic acid decreased endothelium-dependent relaxation elicited by ACh. The inhibitory effect was attenuated by superoxide dismutase. Stearic acid reduced ACh-mediated NO release (Edirisinghe, McCormick Hallam, & Kappagoda, 2006).

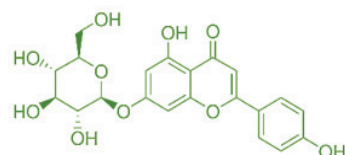
Flavonoids



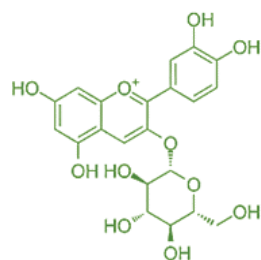
Acacetin



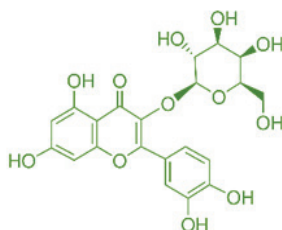
Apigenin



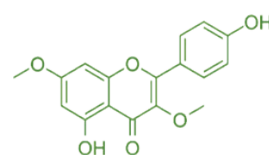
Apigenin 7-O-glucoside



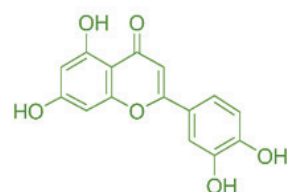
Cyanidin-3-O-glucoside



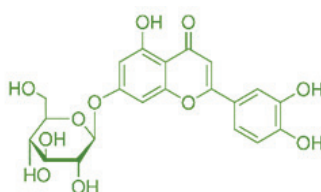
Hyperoside



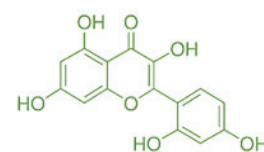
Kumatakenin



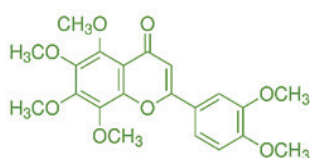
Luteolin



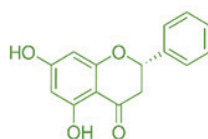
Luteolin 7-O-glucoside



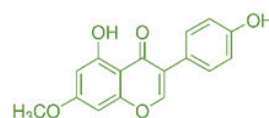
Morin



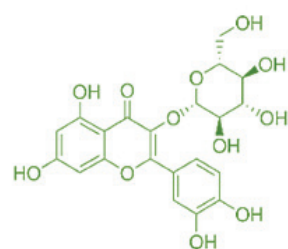
Nobiletin



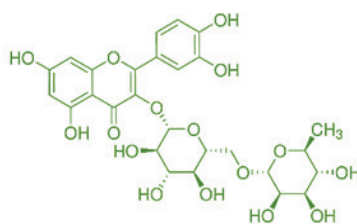
Pinocembrin



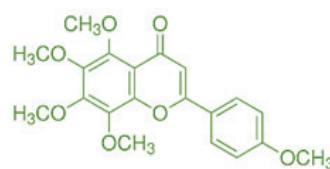
Prunetin



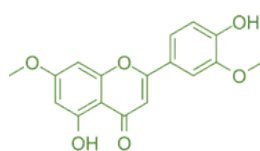
Quercetin-3-O-glucoside



Quercetin-3-O-rutinoside



Tangeretin



Velutin

Figure 6. Flavonoids of *Ficus carica* L. involved in smooth muscle contractility

Acacetin

In SHR, acacetin ameliorated endothelium-dependent vasorelaxation (Li, Y. et al., 2022).

Apigenin

Apigenin caused relaxation of the intrarenal artery through blocking the CaCC channel and activating the K_v channel (Jing et al., 2019). Apigenin produced relaxant responses in tracheal rings. This effect may be related to inhibiting extracellular Ca^{2+} influx and phosphodiesterase (Chen & Ko, 2017). The flavone can behave as a relaxant agent in the thoracic aorta by protecting against oxidative stress (Jin et al., 2009).

Apigenin 7-O-glucoside

Apigenin 7-O-glucoside was identified in *Salvia sclarea* L. methanolic extract. The flavone may contribute to the spasmolytic activity of the extract (Randjelović et al., 2023).

Cyanidin-3-O-glucoside

Cyanidin-3-O-glucoside improved vascular hyporeactivity and endothelium-dependent relaxations induced by peroxynitrite in the thoracic aorta (Serraino et al., 2003).

Hyperoside

Hyperoside could reduce ACh-induced airway smooth muscle contractions (Hake et al., 2022). In middle cerebral arteries, the flavonoid promoted endothelium-dependent and -independent relaxations. Hyperoside-evoked endothelium-dependent relaxation may be associated with endogenous H_2S (Han, Xuan, Hu, & Chen, 2014).

Kumatakenin

Kumatakenin showed myorelaxant activity in the presence of endothelium (Son et al., 2024).

Luteolin

Luteolin had an inhibitory effect on the spontaneous contractions in colonic smooth muscle. BayK8644, an L-type Ca^{2+} channel agonist, significantly mitigated the relaxant responses to luteolin (Yang et al., 2020). Lu-

teolin dose-dependently relaxed PE-contracted aorta, which was partially inhibited by L-NAME treatment. In the aorta contracted with KCl, the relaxant activity of luteolin was reduced but still statistically significant (Si, Wyeth, & Liu, 2014). Luteolin presented relaxation of ACh-contracted ileal smooth muscle (Fleer & Verspohl, 2007). The flavone exhibited a bronchorelaxant effect on tracheal preparations, possibly through phosphodiesterase inhibition and $[Ca^{2+}]_i$ decrease (Ko, Shih, Leu, Chen, & Chang, 2005).

Luteolin 7-O-glucoside

Luteolin 7-O-glucoside enhanced the spontaneous tone and ACh-evoked contractions of jejunal smooth muscle (Mendel et al., 2020). Two extracts of artichoke, including luteolin 7-O-glucoside, showed contrary effects on ileum segments contracted by serotonin (Verspohl et al., 2008).

Morin

Morin exhibited an inhibitory action on vascular $Ca_v1.2$ channels (Carullo et al., 2021). The flavonol promoted the relaxation of the endothelium-intact mesenteric artery through TRPV4 channels (Zhang et al., 2019). The biphasic contractions of the ileum were suppressed by morin (Hammad & Abdalla, 1997).

Nobiletin

Nobiletin induced more relaxant responses against PE administration than KCl administration in aortic rings with endothelium. In the absence of endothelium, ODQ decreased nobiletin-evoked vasorelaxation, whereas IBMX increased it. Treatment with iberiotoxin or glybenclamide caused inhibition in nobiletin-mediated relaxations (Kaneda et al., 2019).

Pinocembrin

Pinocembrin could inhibit Ang II-mediated contractions of the aortic segments without endothelium by downregulating Rho kinase 1 (Li, Yang, Yuan, Zhao, & Du, 2013). The vasorelaxant effect of pinocembrin may be via the blockage of the Ang II- AT_1 - Ca^{2+} -ERK1/2 cascade (Li et al., 2013). The flavanone caused endothelium-dependent relaxation via the

NO-cGMP pathway, relaxing endothelium-denuded aorta by opening K^+ channels and inhibiting Ca^{2+} influx (Zhu, Fang, Li, & Du, 2007).

Prunetin

Prunetin induced relaxation in the aorta via the inhibition of ryanodine receptor, voltage-dependent, and receptor-operated Ca^{2+} channels (Kim, Jo, Choi, & Lee, 2018).

Quercetin-3-O-glucoside

Quercetin-3-O-glucoside, the main compound in the ethyl acetate fraction, could diminish the contraction caused by NE in the internal thoracic artery. The vasorelaxant activity of quercetin-3-O-glucoside was mainly weakened by indomethacin (Malheiros et al., 2022). In the mesenteric vascular bed, the polyphenol was a producer of NO and had an opening effect on K^+ channels such as Kir6.1 and K_{Ca} (Gasparotto Junior, Dos Reis Piornedo, Assreuy, & Da Silva-Santos, 2016). A fraction from *Bidens pilosa* L. var. *radiata* SCHERFF contained hyperin, quercetin-3-O-glucoside, and rutin, which decreased the contractile responses mediated by histamine in the ileum (Matsumoto, Horiuchi, Kamata, & Seyama, 2009). Quercetin-3-O-glucoside, found in a fraction of *Argemone platyceras* Link & Otto, resisted early and late contraction phases induced by the antigen ovalbumin in the trachea. These contractile responses were abolished using indomethacin. It also antagonized leukotriene D₄- or CCh-induced contraction (Fernandez et al., 2005).

Quercetin-3-O-rutinoside

Quercetin-3-O-rutinoside had a suppressive effect on endothelial dysfunction in different types of tissue (de Moraes Campos et al., 2023). In fetal placental vessels of the chorionic plate, quercetin-3-O-rutinoside remained the bradykinin-mediated relaxation, although contracting the effect of H_2O_2 (Sthijns et al., 2017). In high-glucose-treated human umbilical vein EC, the flavonoid altered the levels of Nox and ROS-sensitive NLRP3 and IL-1 β proteins and stimulated NO production. However, it diminished PE-in-

duced contraction and augmented ACh-induced relaxation in the diabetic aorta (Wang, Wu, Sui, Wang, & Qiu, 2017). Quercetin-3-O-rutinoside, a flavonol extracted from *Polygala paniculata* L., caused a decrease in the mean arterial pressure of the anesthetized rats (Lapa et al., 2011).

Tangeretin

Tangeretin resisted KCl-/PE-mediated contractions of the aorta (Ramunno et al., 2024). Tangeretin abolished contractions induced by sphingosylphosphorylcholine in coronary arteries. The vasorelaxant effect may be related to the inhibition of the Fyn/Rho-kinase pathway (Li, Zhang, Morita, Kishi, & Kobayashi, 2022).

Velutin

Velutin was identified as one of the bioactive compounds of *Berberis lycium* Royle. The herb exerted spasmolytic and bronchorelaxant activities (Hussain & Aleem, 2023).

Organic acids

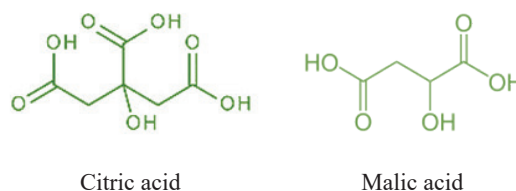


Figure 7. Organic acids of *Ficus carica* L. involved in smooth muscle contractility

Citric acid

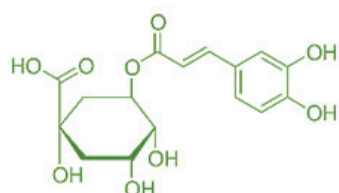
Citric acid relaxed contractions of endothelium-intact aortic rings, which were isolated from SHR. This effect was reduced by endothelium removal (Nakamura, Suzuki, Goto, Yamaguchi, & Hiramitsu, 2023). Citric acid caused contractions of detrusor smooth muscle via Ca^{2+} channel activity (Dasgupta, Elliott, & Tincello, 2009). Inhalation of citric acid elicited bronchoconstriction partly through bradykinin and tachykinin. However, the contraction was decreased by citric acid-mediated NO release (Ricciardolo et al., 1999).

Malic acid

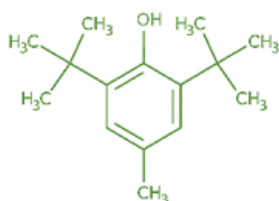
The hydroethanolic extract obtained from *Citrus lanatus* L. seed also contained malic acid along

with many bioactive compounds and exerted spasmolytic activities (Wahid, Saqib, Qamar, & Ziora, 2022).

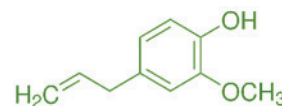
Phenolic compounds



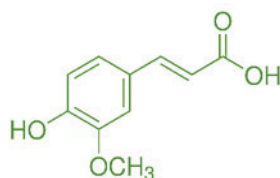
Chlorogenic acid



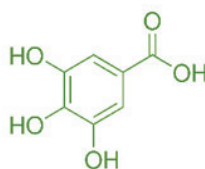
2,6-Di-tert-butyl-4-methylphenol



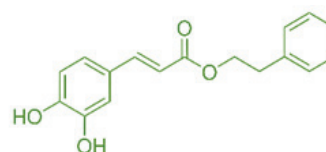
Eugenol



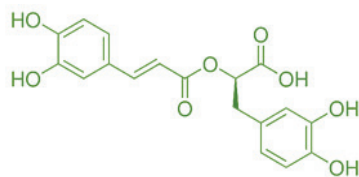
Ferulic acid



Gallic acid



Phenethyl caffeate



Rosmarinic acid

Figure 8. Phenolic compounds of *Ficus carica* L. involved in smooth muscle contractility

Chlorogenic acids (3-*O*-Caffeoylquinic acid and 5-*O*-Caffeoylquinic acid)

Chlorogenic acid could reduce ROS levels and improve NO bioavailability in human umbilical vein EC, as well as the aorta from diabetic rats. It protected against hyperglycemia-induced vascular endothelial dysfunction. The effect of chlorogenic acid was concerned with the increase of Nrf2 expression and the decrease of P22^{phox}, P47^{phox}, P67^{phox}, and nitrotyrosine levels (Wang et al., 2021). Chlorogenic acid resisted bladder contraction with CCh. The phenolic acid displayed its inhibitory effect through activating adenylyl cyclase (Kaneda, Sasaki, Urakawa, & Shimizu, 2018). Chlorogenic acid, a phenolic compound from the methanolic extract of *Inula viscosa* L., caused relaxation of the aorta contracted by PE (Hakkou et al.,

2017). It blunted PE-induced contractions in the aorta with intact endothelium. However, the inhibitory activity was significantly diminished by L-NAME rather than the indomethacin and apamin/charybdotoxin combination. Thus, the compound revealed endothelium-dependent relaxation via NOS, COX, and EDRF pathways. 10⁻⁶ M chlorogenic acid promoted relaxation responses produced by ACh, whereas 10⁻⁴ M chlorogenic acid alleviated ACh- and bradykinin-induced vasorelaxation. 10⁻⁶ M and 10⁻⁴ M chlorogenic acid caused relaxation on contractile responses mediated by PE (Tom, Girard-Thernier, & Demougeot, 2016). Chlorogenic acid, which was found in pomegranate juice, showed a relaxant effect on the corpora cavernosa only at the highest dose (Oztekin et al., 2014).

2,6-Di-tert-butyl-4-methylphenol

2,6-Di-tert-butyl-4-methylphenol, a phenolic antioxidant, was identified in *Panicum miliaceum* L. extracts that had myorelaxant effects on the aorta, trachea, and jejunum (Saqib et al., 2022).

Eugenol

Eugenol interfered with bladder phasic and tonic contractions evoked by high K^+ or CCh. Moreover, the compound abolished contractile responses against $BaCl_2$. The spasmolytic activities of eugenol may be related to the inhibition of M_3 muscarinic receptors and/or VDCC (Araújo et al., 2024). Eugenol impaired arsenic- and mercury-constricted tracheal rings. This bronchorelaxant effect was diminished by L-NAME and verapamil (Kundu, Shabir, Basir, & Khan, 2016). It decreased contractions in response to intravascular pressure or depolarizing high K^+ in cerebral arteries through VDCC (Peixoto-Neves, Leal-Cardoso, & Jaggar, 2014). Eugenol dilated the aorta contracted with arsenic and mercury via the induction of NO formation and the inhibition of ROS generation (Kundu, Shabir, Basir, & Khan, 2014). Eugenol had antispasmodic activity on ileum preparations (Leal-Cardoso et al., 2002).

Ferulic acid

Ferulic acid led to relaxation in the aorta, small mesentery, and coronary artery. The relaxant activity of ferulic acid was related to inhibition of VDCC and dephosphorylation of ERK/ROCK/MYPT1-related Ca^{2+} sensitization signaling pathways (Zhou et al., 2017). It exerted vasoprotective activity in rats supplemented with fructose (El-Bassossy, Badawy, Nea-

Phenylpropanoids

matallah, & Fahmy, 2016). The phenolic acid stimulated NO production and had an excitatory effect on ACh-induced relaxation of the aorta precontracted with PE in diabetic rats (Badawy, El-Bassossy, Fahmy, & Azhar, 2013).

Gallic acid

Gallic acid caused relaxation in aortic segments with endothelium through NO release and K^+ channel activation. It induced endothelium-independent relaxation by inhibiting Ca^{2+} channels (de Oliveira et al., 2016). The phenolic acid produced contractile responses in the aortae by suppressing NO-mediated relaxation (Sanae, Miyaichi, & Hayashi, 2002).

Phenethyl caffeate

Phenethyl caffeate relaxed spontaneous ileal smooth muscle contractions, which were inhibited by nifedipine and EDTA. The compound decreased KCl-mediated contractions (Aviello et al., 2010). Endothelial NO and β -adrenoceptors accompanied the relaxant effects of phenethyl caffeate in coronary arteries (Long et al., 2009). High-dose phenethyl caffeate showed vasorelaxant activity in endothelium-denuded aortic segments, possibly via blocking Ca^{2+} channels. L-NAME partially abolished phenethyl caffeate-induced relaxations (Cicala et al., 2003).

Rosmarinic acid

In hypertensive rats, rosmarinic acid could mitigate systolic blood pressure by inhibiting ACE (Ferreira et al., 2018). Rosmarinic acid did not alter ACh-evoked ileal smooth muscle contractions (Demirezer et al., 2015).

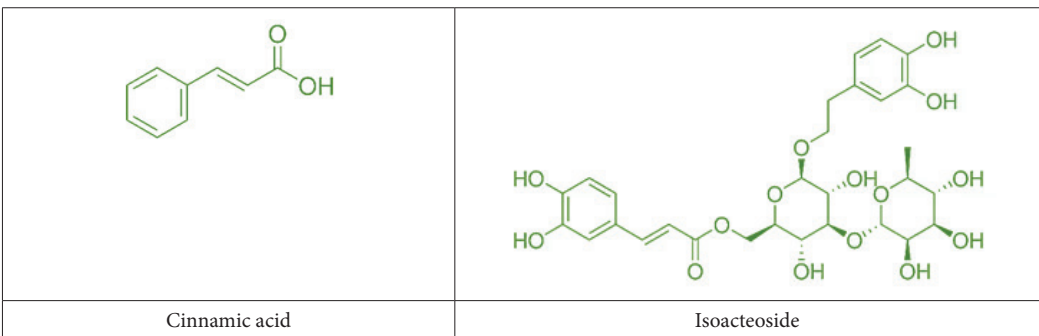


Figure 9. Phenylpropanoids of *Ficus carica* L. involved in smooth muscle contractility

Cinnamic acid

Cinnamic acid induced relaxing effects in the thoracic aorta through the NO/cGMP/PKG signaling pathway (Kang, Kang, & Shin, 2013).

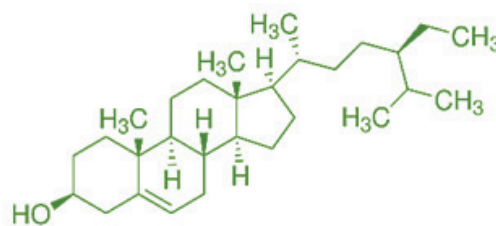
Isoacteoside

Isoacteoside could not depress ACh-mediated contractions in the ileum (Fleer & Verspohl, 2007).

Beta-sitosterol

β -sitosterol depressed PE-induced contractions of aortic segments, which were inhibited by L-NAME treatment and endothelial removal. Moreover, this phytosterol triggered NO production in aortae (Abdallah et al., 2021).

Phytosterol



β -Sitosterol

Figure 10. Phytosterol of *Ficus carica* L. involved in smooth muscle contractility

Terpenes

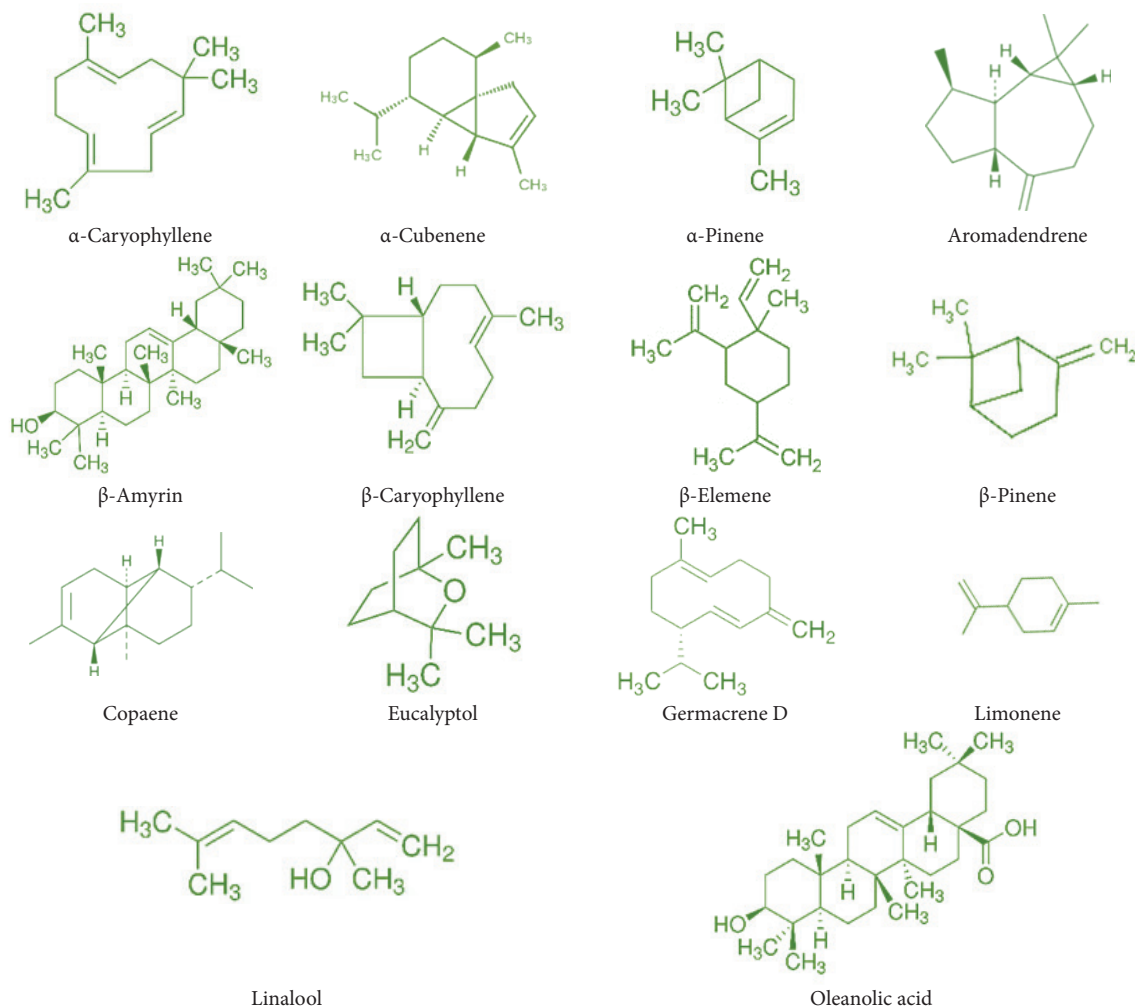


Figure 11. Terpenes of *Ficus carica* L. involved in smooth muscle contractility

Alpha-caryophyllene

α -Caryophyllene is the major component of *Nepeta cataria* L. essential oil. The oil led to the abolition of spontaneous contractions of jejunal smooth muscle, comparable to that of papaverine and verapamil. It relaxed KCl-evoked contractions, similar to papaverine. Incubation with the oil elicited a rightward parallel shift in high K^+ and Ca^{2+} -free medium, comparable to the effects of papaverine and verapamil. In contracted tracheal rings with KCl or CCh, the oil caused relaxation. The effect was similar to papaverine. The treatment of the oil contributed to the isoprenaline-induced concentration-response curve in contractions evoked by CCh, comparable to papaverine (Gilani et al., 2009).

Alpha-cubenene

Valeriana pilosa Ruiz & Pav. essential oil, which is α -cubenene, one of its major compounds, diminished spasmolytic action by antagonizing cholinergic receptors and Ca^{2+} channels in ileum segments (Ybañez-Juica et al., 2023).

Alpha-pinene

α -Pinene caused relaxation in the superior mesenteric artery through the endothelium, TRPA1 channel activity, NO release, and sGC stimulation (Jin et al., 2023). It augmented ACh- and KCl-evoked contractions in tracheal smooth muscle (Lima et al., 2010). The monoterpene showed an inhibitory effect on the resting tonus of the ileum. ACh-/KCl-stimulated contractions were reduced by α -pinene (Câmara, Nascimento, Macêdo-Filho, Almeida, & Fonteles, 2003).

Aromadendrene

Aromadendrene is one of the main constituents of mint oil and could contribute to attenuating the tonus in aortic preparations (Alkharfy et al., 2024). The aromadendrene-containing fractions of *Eucalyptus camaldulensis* Dehnh. caused bronchorelaxation in the tracheal chains contracted by PE. The efficacy of the most relaxing fraction was associated with the inhibition of Ca^{2+} channels (Kheder, Al-Habib, Gilar-doni, & Vidari, 2020).

Beta-amyrin

β -Amyrin had spasmolytic activities on the ileum (Akinmurele et al., 2023).

Beta-caryophyllene

In epithelium-intact tracheal segments, β -caryophyllene (0.05-50 mM) caused an impairment of myogenic tone. It promoted relaxation of epithelium-intact and -deprived tracheal segments contracted with high K^+ or ACh. At higher doses, the sesquiterpene potentiated ACh-induced contractions. It was determined that β -caryophyllene blocked extracellular Ca^{2+} currents via VDCC using the patch-clamp technique (Pinho-da-Silva et al., 2012). β -Caryophyllene altered the baseline tonus of ileal smooth muscle and presented antispasmodic action through the blockade of extracellular Ca^{2+} influx (Leonhardt et al., 2010). Two samples of the essential oil from *Croton sonderianus* Müll.Arg., including β -caryophyllene, had an opposing effect on the tracheal basal tonus. Moreover, they decreased contractions in response to KCl and ACh (Pinho-da-Silva et al., 2010).

Beta-elemene

Mentha longifolia L., which is β -elemene from its components, suppressed PE-evoked contractions in the aorta. This relaxing effect was inhibited with glibenclamide, an ATP-sensitive K^+ channel blocker (Alkharfy et al., 2024).

Beta-pinene

β -Pinene had an excitatory effect on ACh- and KCl-mediated contractions of the trachea (Lima et al., 2010). The monoterpene decreased contractions in the ileum induced with serotonin. The spasmolytic action may be related to 5-HT₃ receptor channel inhibition (Riyazi et al., 2007).

Copaene

Copaene may reduce serotonin-induced contractile responses in the ileum by inhibiting cation influx via the 5-HT₃ ligand-gated ion channel (Riyazi et al., 2007).

Eucalyptol

Eucalyptol induced relaxation in mesenteric arteries contracted by high K^+ , PE, or U46619 (Haam et al., 2022). Treatment with eucalyptol decreased KCl- and CCh-evoked contractions in tracheal chains exposed to cigarette smoke. The concentration-contraction curve of $BaCl_2$ was inhibited by eucalyptol (Kenedy-Feitosa et al., 2020). The treatment with eucalyptol significantly dilated PE-stimulated contractions of the aorta in the presence of than in the absence of endothelium. The vasorelaxant effect of eucalyptol was reduced by L-NAME (Pinto et al., 2009). The organic compound diminished the tonic contraction of KCl-induced uterine smooth muscle in a concentration-dependent manner (Ponce-Monter et al., 2008).

Germacrene D

Germacrene D was found in the composition of essential oil from *Lippia thymoides* Mart. & Schauer, which induced myorelaxant activity in the aorta, uterus, and trachea (Silva et al., 2016).

Limonene

Few studies suggested the effects of limonene on various smooth muscle types. Limonene produced relaxant responses in KCl-, ACh-, oxytocin-, and serotonin-contracted uterine smooth muscles. These effects may be related to the blockage of L-type VDCC (Pereira-de-Morais et al., 2019). Limonene enhanced the basal vascular tone; however, it relaxed contractions evoked by KCl in endothelium-intact and -denuded aorta. This compound showed an excitatory or inhibitory effect in endothelium-intact aortic segments induced by PE to its dose amounts. The monoterpene reduced contractions induced by the PKC activator phorbol 12, 13-dibutyrate while it caused a partial inhibition of the L-type VDCC activator BayK-8644-induced contractions (Cardoso-Teixeira et al., 2018). It did not cause a significant change in tracheal smooth muscle resting tone. Limonene inhibited KCl-mediated contractions of the trachea but did not modulate contractile responses evoked by ACh and $BaCl_2$. Therefore, the bronchorelaxant activity of lim-

onene may be associated with VDCC (Carvalho et al., 2017). Limonene dose-dependently exerted myorelaxant activity in the ileum contracted with KCl, ACh, and EFS (Sadraei, Asghari, & Kasiri, 2015).

Linalool

Linalool-rich essential oil extracted from *Lippia alba* (Mill.) N. E. Brown interfered with ACh and Ca^{2+} -mediated contractions in the intestine in a dose-dependent manner (Blanco et al., 2013).

Oleanolic acid

Oleanolic acid caused endothelium-related relaxation through the COX pathway; however, it elicited the relaxation activity of endothelium-independent through K_v and K_{ATP} channels (Madlala et al., 2016). Oleanolic acid possessed a vasorelaxant action. The underlying mechanism consisted of endothelium-mediated NO release and the decrease of Ca^{2+} levels in VSMC. The compound induced eNOS-Ser phosphorylation via PI3K/Akt signaling pathways (Rodriguez-Rodriguez et al., 2008).

CONCLUSION

F. carica is a medicinal plant that has been used since ancient times. The therapeutic properties may be related to the presence of the chemical compounds in it. Phytochemical studies showed that figs contain several bioactive compounds in different chemical classes, such as alcohols, aldehydes, organic acids, ketones, coumarins, hydrocarbons, esters, phenolic compounds, fatty acids, terpenes, phytosterols, and flavonoids. This review presented the effects of *F. carica* and its phytochemical constituents on smooth muscle contraction-relaxation responses. We detected that 64 components identified from different parts of *F. carica* are involved in smooth muscle excitability. In this regard, fig exerts anti-constipation, antispasmodic, and hypotensive actions. Due to its pharmacological activities, *F. carica* may be a drug candidate for diseases related to smooth muscle dysfunction, including hypertension, atherosclerosis, chronic obstructive pulmonary disease, asthma, gastrointestinal

motility, and inflammatory bowel diseases. However, further clinical and animal model studies are needed to elucidate the effects of *F. carica* and its compounds on smooth muscle contractility.

AUTHOR CONTRIBUTION STATEMENT

Conceptualization (SD, INS), Literature search (INS), Writing (SD, INS), Supervision (SD)

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

- Abdallah, H. M., Timraz, N. Z., Ibrahim, S. R. M., El-Halawany, A. M., Malebari, A. M., Shehata, I. A., & El-Bassossy, H. M. (2021). Nitric-oxide-mediated vasodilation of bioactive compounds isolated from *Hypericum revolutum* in rat aorta. *Biology*, 10(6), 541. doi:10.3390/biology10060541
- Abraham, W. M., Abraham, M. K., & Ahmed, T. (1996). Protective effect of heparin on immunologically induced tracheal smooth muscle contraction in vitro. *International Archives of Allergy and Immunology*, 110(1), 79-84. doi:10.1159/000237315
- Akinmurele, O. J., Sonibare, M. A., Elujoba, A. A., Ogunlakin, A. D., Yeye, O. E., Gyebi, G. A.,... Al-anzi, A. R. (2023). Antispasmodic effect of *Alstonia boonei* De Wild. and its constituents: Ex vivo and in silico approaches. *Molecules*, 28(20), 7069. doi:10.3390/molecules28207069,
- Alamgeer, Iman, S., Asif, H., & Saleem, M. (2017). Evaluation of antihypertensive potential of *Ficus carica* fruit. *Pharmaceutical Biology*, 55(1), 1047-1053. doi:10.1080/13880209.2017.1278611
- Alkharfy, K. M., Ahmad, A., Almuaijel, S., Bin Hashim, A., Raish, M., Jan, B. L.,... Alajmi, M. F. (2024). The vascular effects of peppermint (*Mentha longifolia* L.) on aorta in a mouse model: An ex-vivo and computational study. *Journal of Biomolecular Structure & Dynamics*, 44(5), 2312-2327. doi:10.1080/07391102.2024.2439616
- Allahyari, S., Delazar, A., & Najafi, M. (2014). Evaluation of general toxicity, anti-oxidant activity and effects of *Ficus Carica* leaves extract on ischemia/reperfusion injuries in isolated heart of rat. *Advanced Pharmaceutical Bulletin*, 4(Suppl 2), 577-582. doi:10.5681/apb.2014.085
- Alvarez-Collazo, J., Alonso-Carbajo, L., López-Medina, A. I., Alpizar, Y. A., Tajada, S., Nilius, B.,... Alvarez, J. L. (2014). Cinnamaldehyde inhibits L-type calcium channels in mouse ventricular cardiomyocytes and vascular smooth muscle cells. *Pflugers Archiv*, 466(11), 2089-2099. doi:10.1007/s00424-014-1472-8
- Amani, S., Mohebodini, M., Khademvatan, S., Jafari, M., & Kumar, V. (2021). *Piriformospora indica* based elicitation for overproduction of phenolic compounds by hairy root cultures of *Ficus carica*. *Journal of Biotechnology*, 327, 43-53. doi:10.1016/j.jbiotec.2020.12.015
- Amani, S., Mohebodini, M., Khademvatan, S., Jafari, M., & Kumar, V. (2024). Modifications in gene expression and phenolic compounds content by methyl jasmonate and fungal elicitors in *Ficus carica*. Cv. Siah hairy root cultures. *BMC Plant Biology*, 24(1), 520. doi:10.1186/s12870-024-05178-2
- Amato, A., Liotta, R., & Mulè, F. (2014). Effects of menthol on circular smooth muscle of human colon: Analysis of the mechanism of action. *European Journal of Pharmacology*, 740, 295-301. doi:10.1016/j.ejphar.2014.07.018
- Araújo, M. C., Pereira-Gonçalves, Á., Cardeal Dos Santos, A. N., Freire, J. E. D. C., Peireira-de-Morais, L., Henrique-Félix, F. S.,... Coelho-de-Souza, A. N. (2024). Effect of eugenol on detrusor muscle: Potential for overactive bladder treatment. *International Neurourology Journal*, 28(4), 253-263. doi:10.5213/inj.2448326.163

- Aslam, H., Khan, A. U., Qazi, N. G., Ali, F., Hassan, S. S. U., & Bungau, S. (2022). Pharmacological basis of bergapten in gastrointestinal diseases focusing on H⁺/K⁺ ATPase and voltage-gated calcium channel inhibition: A toxicological evaluation on vital organs. *Frontiers in Pharmacology*, 13, 1005154. doi:10.3389/fphar.2022.1005154
- Aviello, G., Scalisi, C., Fileccia, R., Capasso, R., Romano, B., Izzo, A. A., & Borrelli, F. (2010). Inhibitory effect of caffeic acid phenethyl ester, a plant-derived polyphenolic compound on rat intestinal contractility. *European Journal of Pharmacology*, 640(1-3), 163-167. doi:10.1016/j.ejphar.2010.04.040
- Aysin, F., Simsek Ozek, N., Acet, N., & Koc, K. (2024). The anti-proliferative effects of *Ficus carica* latex on cancer and normal cells. *Journal of Anatolian Environmental and Animal Sciences*, 9(2), 145-151. doi:10.35229/jaes.1412816
- Badawy, D., El-Bassossy, H. M., Fahmy, A., & Azhar, A. (2013). Aldose reductase inhibitors zopolrestat and ferulic acid alleviate hypertension associated with diabetes: Effect on vascular reactivity. *Canadian Journal of Physiology and Pharmacology*, 91(2), 101-7. doi:10.1139/cjpp-2012-0232
- Badgujar, S. B., Patel, V. V., Bandivdekar, A. H., & Mahajan, R. T. (2014). Traditional uses, phytochemistry and pharmacology of *Ficus carica*: A review. *Pharmaceutical Biology*, 52(11), 1487-1503. doi:10.3109/13880209.2014.892515
- Baek, H. I., Ha, K. C., Kim, H. M., Choi, E. K., Park, E. O., Park, B. H.,...Chae, S. W. (2016). Randomized, double-blind, placebo-controlled trial of *Ficus carica* paste for the management of functional constipation. *Asia Pacific Journal of Clinical Nutrition*, 25(3), 487-96. doi:10.6133/apjcn.092015.06
- Bai, X. J., Tian, H. Y., Wang, T. Z., Du, Y., Xi, Y. T., Wu, Y.,...Ma, A. Q. (2013). Oleic acid inhibits the K(ATP) channel subunit Kir6.1 and the K(ATP) current in human umbilical artery smooth muscle cells. *The American Journal of the Medical Sciences*, 346(3), 204-10. doi:10.1097/maj.0b013e-31826ba186
- Barolo, M. I., Ruiz Mostacero, N., & López, S. N. (2014). *Ficus carica* L. (Moraceae): An ancient source of food and health. *Food Chemistry*, 164, 119-127. doi:10.1016/j.foodchem.2014.04.112
- Bass, V. L., Snow, S., Soukup, J., Schladweiler, M., Ghio, A., Kodavanti, U., & Madden, M. C. (2019). 12-Hydroxy oleic acid impairs endothelium-dependent vasorelaxation. *Journal of Toxicology and Environment Health, Part A*, 82(5), 383-386. doi:10.1080/15287394.2019.1603282
- Bass, V. L., Soukup, J. M., Ghio, A. J., & Madden, M. C. (2020). Oleic acid and derivatives affect human endothelial cell mitochondrial function and vasoactive mediator production. *Lipids in Health and Disease*, 19(1), 128. doi:10.1186/s12944-020-01296-6
- Bény, J. L., & Schaad, O. (2000). An evaluation of potassium ions as endothelium-derived hyperpolarizing factor in porcine coronary arteries. *British Journal of Pharmacology*, 131(5), 965-73. doi:10.1038/sj.bjp.0703658
- Blanco, M. A., Colareda, G. A., van Baren, C., Bandoni, A. L., Ringuelet, J., & Consolini, A. E. (2013). Antispasmodic effects and composition of the essential oils from two South American chemotypes of *Lippia alba*. *Journal of Ethnopharmacology*, 149(3), 803-809. doi:10.1016/j.jep.2013.08.007

- Bouyahya, A., Ben Said, M., Bakri, Y., & Dakka, N. (2016). Phytochemistry and ethnopharmacology of *Ficus carica*. *International Journal of Biochemistry Research & Review*, 14(1), 1-12. doi:10.9734/ijbcr/2016/29029
- Braunstein, T. H., Inoue, R., Cribbs, L., Oike, M., Ito, Y., Holstein-Rathlou, N. H., & Jensen, L. J. (2009). The role of L- and T-type calcium channels in local and remote calcium responses in rat mesenteric terminal arterioles. *Journal of Vascular Research*, 46(2), 138-51. doi:10.1159/000151767
- Calani, L., Bresciani, L., Rodolfi, M., Del Rio, D., Petrucci, R., Faraloni, C., & Ganino, T. (2022). Characterization of the (poly)phenolic fraction of fig peel: Comparison among twelve cultivars harvested in Tuscany. *Plants*, 11(22), 3073. doi:10.3390/plants11223073
- Câmara, C. C., Nascimento, N. R., Macêdo-Filho, C. L., Almeida, F. B., & Fonteles, M. C. (2003). Antispasmodic effect of the essential oil of *Plectranthus barbatus* and some major constituents on the guinea-pig ileum. *Planta Medica*, 69(12), 1080-1085. doi:10.1055/s-2003-45186
- Cardoso-Teixeira, A. C., Ferreira-da-Silva, F. W., Peixoto-Neves, D., Oliveira-Abreu, K., Pereira-Gonçalves, Á., Coelho-de-Souza, A. N., & Leal-Cardoso, J. H. (2018). Hydroxyl group and vasorelaxant effects of perillyl alcohol, carveol, limonene on aorta smooth muscle of rats. *Molecules*, 23(6), 1430. doi:10.3390/molecules23061430
- Carullo, G., Ahmed, A., Trezza, A., Spiga, O., Brizzi, A., Saponara, S.,... Aiello, F. (2021). A multitarget semi-synthetic derivative of the flavonoid morin with improved in vitro vasorelaxant activity: Role of CaV1.2 and KCa1.1 channels. *Biochemical Pharmacology*, 185, 114429. doi:10.1016/j.bcp.2021.114429
- Carvalho, P. M. M., Macêdo, C. A. F., Ribeiro, T. F., Silva, A. A., Da Silva, R. E. R., de Moraes, L. P.,... Barbosa, R. (2017). Effect of the *Lippia alba* (Mill.) N.E. Brown essential oil and its main constituents, citral and limonene, on the tracheal smooth muscle of rats. *Biotechnology Reports*, 17, 31-34. doi:10.1016/j.btre.2017.12.002
- Chaud, M., Franchi, A. M., Gimeno, M. F., & Gimeno, A. L. (1988). Gamma-linolenic acid improves the constancy of contractions in uteri from sprayed rats and is metabolized to prostaglandin E1 but not to bisenoic prostanoids. *Prostaglandins*, 35(1), 95-106. doi:10.1016/0090-6980(88)90277-8
- Cheang, W. S., Lam, M. Y., Wong, W. T., Tian, X. Y., Lau, C. W., Zhu, Z.,...Huang, Y. (2013). Menthol relaxes rat aortae, mesenteric and coronary arteries by inhibiting calcium influx. *European Journal of Pharmacology*, 702(1-3), 79-84. doi:10.1016/j.ejphar.2013.01.028
- Chen, J. L., & Ko, W. C. (2017). Relaxation of isolated guinea-pig trachea by apigenin, a constituent of celery, via inhibition of phosphodiesterase. *European Journal of Pharmacology*, 811, 129-133. doi:10.1016/j.ejphar.2017.06.014
- Chiou, W. F., Huang, Y. L., Chen, C. F., & Chen, C. C. (2001). Vasorelaxing effect of coumarins from *Cnidium monnieri* on rabbit corpus cavernosum. *Planta Medica*, 67(3), 282-284. doi:10.1055/s-2001-12013
- Cicala, C., Morello, S., Iorio, C., Capasso, R., Borrelli, F., & Mascolo, N. (2003). Vascular effects of caffeic acid phenethyl ester (CAPE) on isolated rat thoracic aorta. *Life Sciences*, 73(1), 73-80. doi:10.1016/s0024-3205(03)00235-2

- Daci, A., Ozen, G., Karaman, E. F., Teskin, O., Caglayan, M., Celik, Z.,...Topal, G. (2020). In vitro effects of eicosapentaenoic and docosahexaenoic acid on the vascular tone of a human saphenous vein: Influence of precontractile agents. *Annals of Vascular Surgery*, 64, 318-327. doi:10.1016/j.avsg.2019.09.024
- Dasgupta, J., Elliott, R. A., & Tincello, D. G. (2009). Modification of rat detrusor muscle contraction by ascorbic acid and citric acid involving enhanced neurotransmitter release and Ca²⁺ influx. *Neurourology and Urodynamics*, 28(6), 542-548. doi:10.1002/nau.20701
- Davda, R. K., Stepniakowski, K. T., Lu, G., Ullian, M. E., Goodfriend, T. L., Egan, B. M. (1995). Oleic acid inhibits endothelial nitric oxide synthase by a protein kinase C-independent mechanism. *Hypertension*, 26(5), 764-70. doi:10.1161/01.hyp.26.5.764
- de Oliveira, L. M., de Oliveira, T. S., da Costa, R. M., de Souza Gil, E., Costa, E. A., Passaglia, RdeC.,... Ghedini, P. C. (2016). The vasorelaxant effect of gallic acid involves endothelium-dependent and -independent mechanisms. *Vascular Pharmacology*, 81, 69-74. doi:10.1016/j.vph.2015.10.010
- Demirel, S. (2024). Vasorelaxant effects of biochemical constituents of various medicinal plants and their benefits in diabetes. *World Journal of Diabetes*, 15(6), 1122-1141. doi:10.4239/wjd.v15.i6.1122
- Demirezer, L. Ö., Gürbüz, P., Kelicen Uğur, E. P., Bodur, M., Özenver, N., Uz, A., & Güvenalp, Z. (2015). Molecular docking and ex vivo and in vitro anticholinesterase activity studies of *Salvia* sp. and highlighted rosmarinic acid. *Turkish Journal of Medical Sciences*, 45(5), 1141-1148. doi:10.3906/sag-1404-42
- de Moraes Campos, R., Lima, L. M. A. L. L., da Silva, A. G., Santiago, R. O., Paz, I. A., Cabral, P. H. B.,...do Nascimento, N. R. F. (2023). Rutin ameliorates nitrenergic and endothelial dysfunction on vessels and corpora cavernosa of diabetic animals. *Research in Veterinary Science*, 161, 163-172. doi:10.1016/j.rvsc.2023.06.020
- Dolen, U. C., Sungur, N., Koca, G., Ertunc, O., Bagci Bosi, A. T., Kocer, U., & Korkmaz, M. (2015). The vasodilator effect of a cream containing 10% menthol and 15% methyl salicylate on random-pattern skin flaps in rats. *Archives of Plastic Surgery*, 42(6), 695-703. doi:10.5999/aps.2015.42.6.695
- Edirisinghe, I., McCormick Hallam, K., & Kappagoda, C. T. (2006). Effect of fatty acids on endothelium-dependent relaxation in the rabbit aorta. *Clinical Science*, 111(2), 145-151. doi:10.1042/cs20060001
- El-Bassossy, H., Badawy, D., Neamatallah, T., & Fahmy, A. (2016). Ferulic acid, a natural polyphenol, alleviates insulin resistance and hypertension in fructose fed rats: Effect on endothelial-dependent relaxation. *Chemico-Biological Interactions*, 254, 191-7. doi:10.1016/j.cbi.2016.06.013
- Ergul, M., Ergul, M., Eruygur, N., Atas, M., & Ucar, E. (2019). In vitro evaluation of the chemical composition and various biological activities of *Ficus carica* leaf extracts. *Turkish Journal of Pharmaceutical Sciences*, 16(4), 401-409. doi:10.4274/tjps.galenos.2018.70037
- Fazel, M. F., Abu, I. F., Mohamad, M. H. N., Mat Daud, N. A., Hasan, A. N., Aboo Bakkar, Z.,...Ismail, A. A. (2024). Physicochemistry, nutritional, and therapeutic potential of *Ficus carica* - A promising nutraceutical. *Drug Design, Development and Therapy*, 18, 1947-1968. doi:10.2147/dddt.s436446

- Fernandez, J., Reyes, R., Ponce, H., Oropeza, M., Vancalsteren, M. R., Jankowski, C., & Campos, M. G. (2005). Isoquercitrin from Argemone platyceras inhibits carbachol and leukotriene D4-induced contraction in guinea-pig airways. *European Journal of Pharmacology*, 522(1-3), 108-15. doi:10.1016/j.ejphar.2005.08.046
- Ferreira, L. G., Evora, P. R. B., Capellini, V. K., Albuquerque, A. A., Carvalho, M. T. M., Gomes, R. A. D. S.,...Celotto, A. C. (2018). Effect of rosmarinic acid on the arterial blood pressure in normotensive and hypertensive rats: Role of ACE. *Phytomedicine*, 38, 158-165. doi:10.1016/j.phymed.2017.02.006
- Fleer, H., & Verspohl, E. J. (2007). Antispasmodic activity of an extract from *Plantago lanceolata* L. and some isolated compounds. *Phytomedicine*, 14(6), 409-415. doi:10.1016/j.phymed.2006.05.006
- Garibaldi, L. A., Schulte, L. A., Nabaes Jodar, D. N., Gomez Carella, D. S., & Kremen, C. (2021). Time to integrate pollinator science into soybean production. *Trends in Ecology & Evolution*, 36(7), 573-575. doi:10.1016/j.tree.2021.03.013
- Gasparotto Junior, A., Dos Reis Piornedo, R., Assreuy, J., & Da Silva-Santos, J. E. (2016). Nitric oxide and Kir6.1 potassium channel mediate isoquercitrin-induced endothelium-dependent and independent vasodilation in the mesenteric arterial bed of rats. *European Journal of Pharmacology*, 788, 328-334. doi:10.1016/j.ejphar.2016.08.006
- Gibernau, M., Buser, H. R., Frey, J. E., & Hossaert-McKee, M. (1997). Volatile compounds from extracts of figs of *Ficus carica*. *Phytochemistry*, 46(2), 241-244. doi:10.1016/S0031-9422(97)00292-6
- Gilani, A. H., Mehmood, M. H., Janbaz, K. H., Khan, A. U., & Saeed, S. A. (2008). Ethnopharmacological studies on antispasmodic and antiplatelet activities of *Ficus carica*. *Journal of Ethnopharmacology*, 119(1), 1-5. doi:10.1016/j.jep.2008.05.040
- Gilani, A. H., Shah, A. J., Zubair, A., Khalid, S., Kiani, J., Ahmed, A.,...Ahmad, V. U. (2009). Chemical composition and mechanisms underlying the spasmolytic and bronchodilatory properties of the essential oil of *Nepeta cataria* L. *Journal of Ethnopharmacology*, 121(3), 405-411. doi:10.1016/j.jep.2008.11.004
- Gond, N. Y., & Khadabadi, S. S. (2008). Hepatoprotective activity of *Ficus carica* leaf extract on rifampicin-induced hepatic damage in rats. *Indian Journal of Pharmaceutical Sciences*, 70(3), 364-366. doi:10.4103/0250-474x.43003
- Gozlekci, S., Kafkas, E., & Ercisli, S. (2011). Volatile compounds determined by HS/GC-MS technique in peel and pulp of Fig (*Ficus carica* L.) cultivars grown in Mediterranean region of Turkey. *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*, 39(2), 105-108. doi:10.15835/nbha3926261
- Gremmels, H., Bevers, L. M., Fledderus, J. O., Braam, B., van Zonneveld, A. J., Verhaar, M. C., & Joles, J. A. (2015). Oleic acid increases mitochondrial reactive oxygen species production and decreases endothelial nitric oxide synthase activity in cultured endothelial cells. *European Journal of Pharmacology*, 751, 67-72. doi:10.1016/j.ejphar.2015.01.005
- Haam, C. E., Byeon, S., Choi, S. J., Lim, S., Choi, S. K., & Lee, Y. H. (2022). Vasodilatory effect of *Alpinia officinarum* extract in rat mesenteric arteries. *Molecules*, 27(9), 2711. doi:10.3390/molecules27092711

- Hajam, T. A., & H, S. (2022). Phytochemistry, biological activities, industrial and traditional uses of fig (*Ficus carica*): A review. *Chemico-Biological Interactions*, 368, 110237. doi:10.1016/j.cbi.2022.110237.
- Han, J., Xuan, J. L., Hu, H. R., & Chen, Z. W. (2014). Effects and mechanisms of hyperoside on vascular endothelium function in middle cerebral arteries of rats ex vivo. *Zhongguo Zhong Yao Za Zhi*, 39(24), 4849-4855.
- Hake, A., Begrow, F., Spiegler, V., Symma, N., Hensel, A., Düfer, M. (2022). Effects of extracts and flavonoids from *Drosera rotundifolia* L. on ciliary beat frequency and murine airway smooth muscle. *Molecules*, 27(19), 6622. doi:10.3390/molecules27196622
- Hakkou, Z., Maciuk, A., Leblais, V., Bouanani, N. E., Mekhfi, H., Bnouham, M., ...Legssyer, A. (2017). Antihypertensive and vasodilator effects of methanolic extract of *Inula viscosa*: biological evaluation and POM analysis of cynarin, chlorogenic acid as potential hypertensive. *Biomedicine & Pharmacotherapy*, 93, 62-69. doi:10.1016/j.biopha.2017.06.015
- Hammad, H. M., & Abdalla, S. S. (1997). Pharmacological effects of selected flavonoids on rat isolated ileum: Structure-activity relationship. *General Pharmacology*, 28(5), 767-771. doi:10.1016/s0306-3623(96)00299-6
- Harris, D., McCulloch, A. I., Kendall, D. A., & Randall, M. D. (2002). Characterization of vasorelaxant responses to anandamide in the rat mesenteric arterial bed. *The Journal of Physiology*, 539(Pt 3), 893-902. doi:10.1113/jphysiol.2001.013489
- Hussain Shah, S. A., & Aleem, A. (2023). Investigations of plausible pharmacodynamics supporting the antispasmodic, bronchodilator, and antidiarrheal activities of *Berberis lycium* Royle. Via in silico, in vitro, and in vivo studies. *Journal of Ethnopharmacology*, 305, 116115. doi:10.1016/j.jep.2022.116115
- Innocenti, G., Bettero, A., & Caporale, G. (1982). Determination of the coumarinic constituents of *Ficus carica* leaves by HPLC. *Il Farmaco; Edizione Scientifica*, 37(7), 475-485.
- Isogai, T., Taki, F., Suzuki, K., Takagi, K., & Satake, T. (1991). Inhibitory effect of dietary administration of eicosapentaenoic acid on the contractions of guinea-pig tracheal smooth muscle induced by leukotriene C4 and D4. *Arzneimittelforschung*, 41(2), 132-7.
- Jack, A. M., Keegan, A., Cotter, M. A., & Cameron, N. E. (2002). Effects of diabetes and evening primrose oil treatment on responses of aorta, corpus cavernosum and mesenteric vasculature in rats. *Life Sciences*, 71(16), 1863-77. doi:10.1016/s0024-3205(02)01912-4
- Jeivad, F., Yassa, N., Ostad, S. N., Hassannejad, Z., Hassanzadeh Gheshlaghi, G., & Sabzevari, O. (2020). *Ficus carica* L. latex: Possible chemo-preventive, apoptotic activity and safety assessment. *Iranian Journal of Pharmaceutical Research*, 19(3), 231-240. doi:10.22037/ijpr.2020.1101151
- Jesus, R. L. C., Silva, I. L. P., Araújo, F. A., Moraes, R. A., Silva, L. B., Brito, D. S.,...Silva, D. F. (2022). 7-Hydroxycoumarin induces vasorelaxation in animals with essential hypertension: Focus on potassium channels and intracellular Ca²⁺ mobilization. *Molecules*, 27(21), 7324. doi:10.3390/molecules27217324

- Jin, B. H., Qian, L. B., Chen, S., Li, J., Wang, H. P., Bruce, I. C.,...Xia, Q. (2009). Apigenin protects endothelium-dependent relaxation of rat aorta against oxidative stress. *European Journal of Pharmacology*, 616(1-3), 200-205. doi:10.1016/j.ejphar.2009.06.020
- Jin, L., Xie, Z., Lorkiewicz, P., Srivastava, S., Bhatnagar, A., & Conklin, D. J. (2023). Endothelial-dependent relaxation of α -pinene and two metabolites, myrtenol and verbenol, in isolated murine blood vessels. *American Journal of Physiology-Heart and Circulatory Physiology*, 325(6), H1446-H1460. doi:10.1152/ajpheart.00380.2023
- Jing, Y., Chen, R., Dong, M., Liu, Y., Hou, X., Guo, P.,... Zhang, M. (2019). Apigenin relaxes rat intrarenal arteries, depresses Ca^{2+} -activated Cl^- currents and augments voltage-dependent K^+ currents of the arterial smooth muscle cells. *Biomedicine & Pharmacotherapy*, 115, 108926. doi:10.1016/j.biopha.2019.108926
- Kahler, C. P., & Du Plooy, W. J. (1998). Effect of gammalinolenic acid, dihomogammalinolenic acid, ascorbyl-6-gammalinolenic acid, and ascorbyl-6-dihomo gammalinolenic acid on histamine- and methacholine-induced contraction of the isolated guinea pig tracheal chain. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 58(4), 327-31. doi:10.1016/s0952-3278(98)90043-6
- Kaneda, H., Otomo, R., Sasaki, N., Omi, T., Sato, T., & Kaneda, T. (2019). Endothelium-independent vasodilator effects of nobiletin in rat aorta. *Journal of Pharmacological Sciences*, 140(1), 48-53. doi:10.1016/j.jphs.2019.04.004
- Kaneda, T., Sasaki, N., Urakawa, N., & Shimizu, K. (2018). Effects of chlorogenic acid on carbachol-induced contraction of mouse urinary bladder. *Journal of Pharmacological Sciences*, 136(1), 26-30. doi:10.1016/j.jphs.2017.12.006
- Kang, Y. H., Yang, I. J., Morgan, K. G., & Shin, H. M. (2012). Cinnamyl alcohol attenuates vasoconstriction by activation of K^+ channels via NO-cGMP-protein kinase G pathway and inhibition of Rho-kinase. *Experimental & Molecular medicine*, 44(12), 749-755. doi:10.3858/emmm.2012.44.12.083
- Kang, Y. H., Kang, J. S., & Shin, H. M. (2013). Vasodilatory effects of cinnamic acid via the nitric oxide-cGMP-PKG pathway in rat thoracic aorta. *Phytotherapy Research*, 27(2), 205-211. doi:10.1002/ptr.4708
- Kassahun Gebremeskel, A., Wijerathne, T. D., Kim, J. H., Kim, M. J., Seo, C. S., Shin, H. K., & Lee, K. P. (2017). *Psoralea corylifolia* extract induces vasodilation in rat arteries through both endothelium-dependent and -independent mechanisms involving inhibition of TRPC3 channel activity and elaboration of prostaglandin. *Pharmaceutical Biology*, 55(1), 2136-2144. doi:10.1080/13880209.2017.1383484
- Keegan, A., Cotter, M. A., & Cameron, N. E. (2001). Corpus cavernosum dysfunction in diabetic rats: Effects of combined alpha-lipoic acid and gamma-linolenic acid treatment. *Diabetes/Metabolism Research and Reviews*, 17(5), 380-6. doi:10.1002/dmrr.215
- Kennedy-Feitosa, E., Oliveira-Melo, P., Evangelista-Costa, E., Serra, D. S., Cavalcante, F. S. Á., da Ponte, E. L.,...Lima, C. C. (2020). Eucalyptol reduces airway hyperresponsiveness in rats following cigarette smoke-exposed. *Pulmonary Pharmacology & Therapeutics*, 61, 101887. doi:10.1016/j.pupt.2020.101887
- Khadabadi, S. S., Gond, N. Y., Ghiware, N. B., & Shendarkar, G. R. (2007). Hepatoprotective effect of *Ficus carica* leaf in chronic hepatitis. *Indian Drugs*, 44(1), 54-57.

- Kheder, D. A., Al-Habib, O. A. M., Gilardoni, G., & Vidari, G. (2020). Components of volatile fractions from *Eucalyptus camaldulensis* leaves from Iraqi-Kurdistan and their potent spasmolytic effects. *Molecules*, 25(4), 804. doi:10.3390/molecules25040804
- Kim, B., Jo, C., Choi, H. Y., & Lee, K. (2018). Prunetin relaxed isolated rat aortic rings by blocking calcium channels. *Molecules*, 23(9), 2372. doi:10.3390/molecules23092372
- Kiralan, M., & Kiralan, S. S. (2023). Sugar and volatile aroma composition of havran siyah incir. *Bahçe*, 52(2), 89-94. doi:10.53471/bahce.1315055
- Ko, W. C., Shih, C. M., Leu, I. J., Chen, T. T., & Chang, J. P. (2005). Mechanisms of relaxant action of luteolin in isolated guinea pig trachea. *Planta Medica*, 71(5), 406-411. doi:10.1055/s-2005-864133
- Komori, K., Ishii, T., Odashiro, T., Itoh, H., Mawatari, K., Okadome, K., & Sugimachi, K. (1995). Eicosapentanoic acid reduces the intimal thickening of autogenous vein grafts and enhances endothelium-derived relaxing factor. *The Journal of Surgical Research*, 59(6), 747-753. doi:10.1006/jsre.1995.1234
- Kundu, S., Shabir, H., Basir, S. F., & Khan, L. A. (2014). Inhibition of As(III) and Hg(II) caused aortic hypercontraction by eugenol, linalool and carvone. *Journal of Smooth Muscle Research*, 50, 93-102. doi:10.1540/jsmr.50.93
- Kundu, S., Shabir, H., Basir, S. F., & Khan, L. A. (2016). Eugenol and carvone as relaxants of arsenic and mercury hypercontracted rat trachea. *Toxicology and Industrial Health*, 32(12), 1935-1941. doi:10.1177/0748233715598266
- Lambole, M., Pittet, P., Koenigsberger, M., Sauser, R., Bény, J. L., & Meister, J. J. (2005). Evidence for signaling via gap junctions from smooth muscle to endothelial cells in rat mesenteric arteries: Possible implication of a second messenger. *Cell Calcium*, 37(4), 311-20. doi:10.1016/j.ceca.2004.11.004
- Lapa, FdaR., Soares, K. C., Rattmann, Y. D., Crestani, S., Missau, F. C., Pizzolatti, M. G.,...Santos, A. R. (2011). Vasorelaxant and hypotensive effects of the extract and the isolated flavonoid rutin obtained from *Polygala paniculata* L. *Journal of Pharmacy and Pharmacology*, 63(6), 875-81. doi:10.1111/j.2042-7158.2010.01240.x
- Leal-Cardoso, J. H., Lahlou, S., Coelho-de-Souza, A. N., Criddle, D. N., Pinto Duarte, G. I., Santos, M. A., & Magalhães, P. J. (2002). Inhibitory actions of eugenol on rat isolated ileum. *Canadian Journal of Physiology and Pharmacology*, 80(9), 901-906. doi:10.1139/y02-117
- Lee, H. Y., Kim, J. H., Jeung, H. W., Lee, C. U., Kim, D. S., Li, B.,...Chae, S. W. (2012). Effects of *Ficus carica* paste on loperamide-induced constipation in rats. *Food and Chemical Toxicology*, 50 (3-4), 895-902. doi:10.1016/j.fct.2011.12.001
- Leonhardt, V., Leal-Cardoso, J. H., Lahlou, S., Albuquerque, A. A., Porto, R. S., Celedônio, N. R.,...Coelho-de-Souza, A. N. (2010). Antispasmodic effects of essential oil of *Pterodon polygalaeflorus* and its main constituent β -caryophyllene on rat isolated ileum. *Fundamental & Clinical Pharmacology*, 24(6), 749-758. doi:10.1111/j.1472-8206.2009.00800.x
- Li, J., Tian, Y-Z., Sun, B-Y., Yang, D., Chen, J-P., & Men, Q-M. (2012). Analysis on volatile constituents in leaves and fruits of *Ficus carica* by GC-MS. *Chinese Herbal Medicines*, 4(1), 63-69. doi:10.3969/j.issn.1674-6384.2012.01.010

- Li, L., Pang, X. B., Chen, B. N., Gao, L., Wang, L., Wang, S. B.,...Du, G. H. (2013). Pinocembrin inhibits angiotensin II-induced vasoconstriction via suppression of the increase of $[Ca^{2+}]_i$ and ERK1/2 activation through blocking AT(1)R in the rat aorta. *Biochemical and Biophysical Research Communications*, 435(1), 69-75. doi:10.1016/j.bbrc.2013.04.039
- Li, L., Yang, H. G., Yuan, T. Y., Zhao, Y., & Du, G. H. (2013). Rho kinase inhibition activity of pinocembrin in rat aortic rings contracted by angiotensin II. *Chinese Journal of Natural Medicines*, 11(3), 258-263. doi:10.1016/s1875-5364(13)60025-4
- Li, N., Zhang, Y., Morita, T., Kishi, H., & Kobayashi, S. (2022). Inhibitory mechanism of tangeretin, a citrus flavone on the sphingosylphosphorylcholine (SPC)-induced vascular smooth muscle contraction. *Journal of Pharmacological Sciences*, 149(4), 189-197. doi:10.1016/j.jphs.2022.05.002
- Li, Y., Dang, Q., Li, Z., Han, C., Yang, Y., Li, M., & Li, P. (2022). Restoration of mitochondrial function is essential in the endothelium-dependent vasodilation induced by acacetin in hypertensive rats. *International Journal of Molecular Sciences*, 23(19), 11350. doi:10.3390/ijms231911350
- Lima, F. J., Brito, T. S., Freire, W. B., Costa, R. C., Linhares, M. I., Sousa, F. C.,...Magalhães, P. J. (2010). The essential oil of *Eucalyptus tereticornis*, and its constituents alpha- and beta-pinene, potentiate acetylcholine-induced contractions in isolated rat trachea. *Fitoterapia*, 81(6), 649-655. doi:10.1016/j.fitote.2010.03.012
- Liu, Y., Li, H., Chen, L., Zhao, H., Liu, J., Gong, S.,...Ren, W. (2023). Mechanism and pharmacodynamic substance basis of raw and wine-processed *Evodia rutaecarpa* on smooth muscle cells of dysmenorrhea mice. *Pain Research & Management*, 2023, 7711988. doi:10.1155/2023/7711988
- Long, Y., Han, M., Chen, J., Tian, X. Z., Chen, Q., & Wang, R. (2009). The vasorelaxant effect of caffeic acid phenethyl ester on porcine coronary artery ring segments. *Vascular Pharmacology*, 51(2-3), 78-83. doi:10.1016/j.vph.2009.03.002
- Madlala, H. P., Metzinger, T., van Heerden, F. R., Mubabayane, C. T., Mubagwa, K., & Dessy, C. (2016). Vascular endothelium-dependent and independent actions of oleanolic acid and its synthetic oleanane derivatives as possible mechanisms for hypotensive effects. *PLoS One*, 11(1), e0147395. doi:10.1371/journal.pone.0147395
- Malheiros, J., Simões, D. M., Antunes, P. E., Figueirinha, A., Cotrim, M. D., & Fonseca, D. A. (2022). Vascular effects of polyphenols from *Agrimonia eupatoria* L. and role of Isoquercitrin in its vasorelaxant potential in human arteries. *Pharmaceuticals*, 15(5), 638. doi:10.3390/ph15050638
- Martínez, G. J. (2008). Farmacopea natural y tratamiento de afecciones de la piel en la medicina tradicional de los campesinos de las sierras de Córdoba (República Argentina). *Dominguezia*, 24, 27-46.
- Martišienė, I., Zigmantaitė, V., Pudžiuvėlytė, L., Bernatoniėnė, J., & Jurevičius, J. (2023). *Elsholtzia ciliata* essential oil exhibits a smooth muscle relaxant effect. *Pharmaceuticals*, 16(10), 1464. doi:10.3390/ph16101464
- Matsumoto, T., Horiuchi, M., Kamata, K., & Seyama, Y. (2009). Effects of *Bidens pilosa* L. var. *radiata* SCHERFF treated with enzyme on histamine-induced contraction of guinea pig ileum and on histamine release from mast cells. *Journal of Smooth Muscle Research*, 45(2-3), 75-86. doi:10.1540/jsmr.45.75

- Matsumoto, T., Nakayama, N., Ishida, K., Kobayashi, T., & Kamata, K. (2009). Eicosapentaenoic acid improves imbalance between vasodilator and vasoconstrictor actions of endothelium-derived factors in mesenteric arteries from rats at chronic stage of type 2 diabetes. *Journal of Pharmacology and Experimental Therapeutics*, 329(1), 324-34. doi:10.1124/jpet.108.148718
- Mawa, S., Husain, K., & Jantan, I. (2013). *Ficus carica* L. (Moraceae): Phytochemistry, traditional uses and biological activities. *Evidence-Based Complementary and Alternative Medicine*, 2013, 974256. doi:10.1155/2013/974256
- Mendel, M., Chłopecka, M., Latek, U., Karlik, W., Tomczykowa, M., Strawa, J., & Tomczyk, M. (2020). Evaluation of the effects of *Bidens tripartita* extracts and their main constituents on intestinal motility - An ex vivo study. *Journal of Ethnopharmacology*, 259, 112982. doi:10.1016/j.jep.2020.112982
- Moers, A., & Schrezenmeir, J. (1997). Palmitic acid but not stearic acid inhibits NO-production in endothelial cells. *Experimental and Clinical Endocrinology & Diabetes*, 105(Suppl 2), 78-80. doi:10.1055/s-0029-1211804
- Mohamad, S., Zin, N. M., Wahab, H. A., Ibrahim, P., Sulaiman, S. F., Zahariluddin, A. S., & Noor, S. S. (2011). Antituberculosis potential of some ethnobotanically selected Malaysian plants. *Journal of Ethnopharmacology*, 133(3), 1021-1026. doi:10.1016/j.jep.2010.11.037
- Morf, T., Bény, J. L., Flammer, J., & Haefliger, I. O. (2002). Effect of palmitoleic acid on bradykinin-induced endothelium-dependent relaxation in isolated pig ciliary artery. *Klinische Monatsblätter für Augenheilkunde*, 219(4), 284-8. doi:10.1055/s-2002-30674
- Morita, S., Sasaki, H., Kaneda, Y., Rogi, T., Izumo, T., & Nakai, M. (2023). Effects of combining docosahexaenoic acid and eicosapentaenoic acid with sesame lignan on vascular endothelial function. *Journal of Nutritional Science and Vitaminology*, 69(5), 370-376. doi:10.3177/jnsv.69.370
- Nakamura, K., Suzuki, Y., Goto, K., Yamaguchi, S., & Hiramitsu, M. (2023). Antihypertensive and vasorelaxant effects of citric acid and lemon juice in spontaneously hypertensive rats: In vivo and ex vivo studies. *Nutrients*, 15(17), 3849. doi:10.3390/nu15173849
- Niu, X. L., Liu, L. Y., Hu, M. L., & Chen, X. (1995). Some similarities in vascular effects of oleic acid and oxidized low-density lipoproteins on rabbit aorta. *Journal of Molecular and Cellular Cardiology*, 27(1), 531-9. doi:10.1016/s0022-2828(08)80048-x
- Nomoto, Y., Yoshida, A., Ikeda, S., Kamikawa, Y., Harada, K., Ohwatashi, A., & Kawahira, K. (2008). Effect of menthol on detrusor smooth-muscle contraction and the micturition reflex in rats. *Urology*, 72(3), 701-705. doi:10.1016/j.urology.2007.11.137
- Nunes, D. O., Almenara, C. C., Broseghini-Filho, G. B., Silva, M. A., Stefanon, I., Vassallo, D. V., & Padilha, A. S. (2014). Flaxseed oil increases aortic reactivity to phenylephrine through reactive oxygen species and the cyclooxygenase-2 pathway in rats. *Journal of Molecular and Cellular Cardiology*, 13, 107. doi:10.1186/1476-511x-13-107
- Obara, K., Kawaguchi, A., Inaba, R., Kawakita, M., Yamaguchi, R., Yamashita, H.,...Tanaka, Y. (2021). Docosahexaenoic acid and eicosapentaenoic acid inhibit the contractile responses of the guinea pig lower gastrointestinal tract. *Biological and Pharmaceutical Bulletin*, 44(8), 1129-1139. doi:10.1248/bpb.b21-00362

- Oliveira, A. P., Valentão, P., Pereira, J. A., Silva, B. M., Tavares, F., & Andrade, P. B. (2009). *Ficus carica* L.: Metabolic and biological screening. *Food and Chemical Toxicology*, 47(11), 2841-2846. doi:10.1016/j.fct.2009.09.004
- Oliveira, A. P., Silva, L. R., Andrad, P. B., Valentão, P., Silva, B. M., Gonçalves, R. F.,...Guedes de Pinho, P. (2010). Further insight into the latex metabolite profile of *Ficus carica*. *Journal of Agricultural and Food Chemistry*, 58(20), 10855-10863. doi:10.1021/jf1031185
- Oztekin, C. V., Gur, S., Abdulkadir, N. A., Kartal, M., Karabakan, M., Akdemir, A. O.,...Cetinkaya, M. (2014). Analysis of pomegranate juice components in rat corpora cavernosa relaxation. *International Journal of Impotence Research*, 26(2), 45-50. doi:10.1038/ijir.2013.33
- Özatalay, G. Z. (2014). Aydın yöresi halk hekimliğinde incir kullanımı. *Karamanoglu Mehmetbey University Journal of Social and Economic Research*, 2014(4), 151-154. doi:10.18493/kmusekad.05098
- Park, Y. R., Eun, J. S., Choi, H. J., Nepal, M., Kim, D. K., Seo, S. Y.,...Soh, Y. (2009). Hexane-soluble fraction of the common fig, *Ficus carica*, inhibits osteoclast differentiation in murine bone marrow-derived macrophages and RAW 264.7 cells. *The Korean Journal of Physiology & Pharmacology*, 13(6), 417-424. doi:10.4196/kjpp.2009.13.6.417
- Patil, V. V., Bhangale, S. C., & Patil, V. R. (2010). Evaluation of anti-pyretic potential of *Ficus carica* leaves. *International Journal of Pharmaceutical Sciences Review and Research*, 2(2), 48-50.
- Peixoto-Neves, D., Leal-Cardoso, J. H., & Jaggar, J. H. (2014). Eugenol dilates rat cerebral arteries by inhibiting smooth muscle cell voltage-dependent calcium channels. *Journal of Cardiovascular Pharmacology*, 64(5), 401-406. doi:10.1097/fjc.0000000000000131
- Pereira-de-Morais, L., Silva, A. A., da Silva, R. E. R., Costa, R. H. S. D., Monteiro, Á. B., Barbosa, C. R. D. S.,...Barbosa, R. (2019). Tocolytic activity of the *Lippia alba* essential oil and its major constituents, citral and limonene, on the isolated uterus of rats. *Chemico-Biological Interactions*, 297, 155-159. doi:10.1016/j.cbi.2018.11.006
- Perveen, F., Khan, F., Irum, Z., Siddiqui, A. H., Bhatti, M., & Iqbal, R. (2021). Anti dyslipidemic effect of *Ficus carica* fruit (fig) on lipid profile of diet induced hyperlipidemic rats. *Pakistan Journal of Medical & Health Sciences*, 15, 1709-1712. doi:10.53350/pjmhs211571709
- Pinho-da-Silva, L., Mendes-Maia, P. V., do Nascimento Garcia, T. M., Cruz, J. S., de Moraes, S. M., Coelho-de-Souza, A. N.,...Leal-Cardoso, J. H. (2010). *Croton sonderianus* essential oil samples distinctly affect rat airway smooth muscle. *Phytomedicine*, 17(10), 721-725. doi:10.1016/j.phymed.2010.01.015.
- Pinho-da-Silva, L., Mendes-Maia, P. V., Teófilo, T. M., Barbosa, R., Ceccatto, V. M., Coelho-de-Souza, A. N.,...Leal-Cardoso, J. H. (2012). trans-Caryophyllene, a natural sesquiterpene, causes tracheal smooth muscle relaxation through blockade of voltage-dependent Ca²⁺ channels. *Molecules*, 17(10), 11965-11977. doi:10.3390/molecules171011965
- Pinto, N. V., Assreuy, A. M., Coelho-de-Souza, A. N., Ceccatto, V. M., Magalhães, P. J., Lahlou, S., Leal-Cardoso, J. H. (2009). Endothelium-dependent vasorelaxant effects of the essential oil from aerial parts of *Alpinia zerumbet* and its main constituent 1,8-cineole in rats. *Phytomedicine*, 16(12), 1151-1155. doi:10.1016/j.phymed.2009.04.007

- Pomposiello, S. I., Alva, M., Wilde, D. W., & Carretero, O. A. (1998). Linoleic acid induces relaxation and hyperpolarization of the pig coronary artery. *Hypertension*, 31(2), 615-620. doi:10.1161/01.hyp.31.2.615
- Ponce-Monter, H., Campos, M. G., Pérez, S., Pérez, C., Zavala, M., Macías, A.,...Cárdenas, N. (2008). Chemical composition and antispasmodic effect of *Casimiroa pringlei* essential oil on rat uterus. *Fitoterapia*, 79(6), 446-450. doi:10.1016/j.fitote.2008.04.005
- Rahmani, A. H., & Aldebasi, Y. H. (2017). *Ficus carica* and its constituents role in management of diseases. *Asian Journal of Pharmaceutical and Clinical Research*, 10(6), 49. doi:10.22159/ajpcr.2017.v10i6.17832
- Ramasamy, S., Parthasarathy, S., & Harrison, D. G. (1998). Regulation of endothelial nitric oxide synthase gene expression by oxidized linoleic acid. *Journal of Lipid Research*, 39(2), 268-76.
- Ramunno, A., Vitale, R. M., Amodeo, P., Crescenzi, C., Panti, A., Fiorenzani, P.,...Fusi, F. (2024). Bioguided identification of polymethoxyflavones as novel vascular CaV1.2 channel blockers from citrus peel. *Molecules*, 29(23), 5693. doi:10.3390/molecules29235693
- Randjelović, M., Branković, S., Jovanović, M., Kitić, N., Živanović, S., Mihajilov-Krstev, T.,...Kitić, D. (2023). An in vitro and in silico characterization of *Salvia sclarea* L. methanolic extracts as spasmolytic agents. *Pharmaceutics*, 15(5), 1376. doi:10.3390/pharmaceutics15051376
- Rasheed, H. M., Khan, T., Wahid, F., Khan, R., & Shah, A. J. (2016). Chemical composition and vascular and intestinal smooth muscle relaxant effects of the essential oil from *Psidium guajava* fruit. *Pharmaceutical Biology*, 54(11), 2679-2684. doi:10.1080/013880209.2016.1178309
- Rasool, I. F. U., Aziz, A., Khalid, W., Koraqi, H., Siddiqui, S. A., Al-Farga, A.,...Ali, A. (2023). Industrial application and health prospective of fig (*Ficus carica*) by-products. *Molecules*, 28(3), 960. doi:10.3390/molecules28030960
- Renda, G., Barut, B., Ceren, R., & Aydin, E. (2023). In vitro tyrosinase inhibitory, DNA interaction studies, and LC-HRMS analysis of *Ficus carica* leaves. *Turkish Journal of Chemistry*, 47(2), 465-475. doi:10.55730/1300-0527.3552
- Ricciardolo, F. L., Rado, V., Fabbri, L. M., Sterk, P. J., Di Maria, G. U., & Geppetti, P. (1999). Bronchoconstriction induced by citric acid inhalation in guinea pigs: Role of tachykinins, bradykinin, and nitric oxide. *American Journal of Respiratory and Critical Care Medicine*, 159(2), 557-562. doi:10.1164/ajrccm.159.2.9804022
- Riyazi, A., Hensel, A., Bauer, K., Geissler, N., Schaaf, S., & Verspohl, E. J. (2007). The effect of the volatile oil from ginger rhizomes (*Zingiber officinale*), its fractions and isolated compounds on the 5-HT₃ receptor complex and the serotonergic system of the rat ileum. *Planta Medica*, 73(4), 355-362. doi:10.1055/s-2007-967171
- Rodriguez-Rodriguez, R., Stankevicius, E., Herrera, M. D., Ostergaard, L., Andersen, M. R., Ruiz-Gutierrez, V., & Simonsen, U. (2008). Oleonic acid induces relaxation and calcium-independent release of endothelium-derived nitric oxide. *British Journal of Pharmacology*, 155(4), 535-46. doi:10.1038/bjp.2008.289
- Ryan, M., McInerney, D., Owens, D., Collins, P., Johnson, A., & Tomki, G. H. (2000). Diabetes and the mediterranean diet: A beneficial effect of oleic acid on insulin sensitivity, adipocyte glucose transport and endothelium-dependent vasoreactivity. *QJM: An International Journal of Medicine*, 93(2), 85-91. doi:10.1093/qjmed/93.2.85

- Sadraei, H., Asghari, G., & Kasiri, F. (2015). Comparison of antispasmodic effects of *Dracocephalum kotschyi* essential oil, limonene and α -terpineol. *Research in Pharmaceutical Sciences*, 10(2), 109-116.
- Saeed, M. A., & Sabir, A. W. (2002). Irritant potential of triterpenoids from *Ficus carica* leaves. *Fitoterapia*, 73(5), 417-420. doi:10.1016/s0367-326x(02)00127-2
- Sanae, F., Miyaichi, Y., & Hayashi, H. (2002). Potentiation of vasoconstrictor response and inhibition of endothelium-dependent vasorelaxation by gallic acid in rat aorta. *Planta Medica*, 68(8), 690-693. doi:10.1055/s-2002-33806
- Sandor, Z. I., Bencsik, T., Dekany, A., & Bartho, L. (2019). Effects of cinnamaldehyde on smooth muscle preparations. *Pharmacology*, 104 (3-4), 207-211. doi:10.1159/000501604.
- Saqib, F., Al-Huqail, A. A., Asma, M., Chicea, L., Hoge, M., Irimie, M., & Gavris, C. (2022). Dose-dependent spasmolytic, bronchodilator, and hypotensive activities of *Panicum miliaceum* L. *Dose-Response*, 20(1), 15593258221079592. doi:10.1177/15593258221079592
- Satoh, K. (2013). Linoleic acid. A novel mechanism of endothelial cell dysfunction. *Circulation Journal*, 77(11), 2702-3. doi:10.1253/circj.13-1155
- Sekine, S., Sasanuki, S., Aoyama, T., & Takeuchi, H. (2007). Lowering systolic blood pressure and increases in vasodilator levels in SHR with oral α -linolenic acid administration. *Journal of Oleo Science*, 56(7), 341-5. doi:10.5650/jos.56.341
- Serraino, I., Dugo, L., Dugo, P., Mondello, L., Mazzon, E., Dugo, G.,...Cuzzocrea, S. (2003). Protective effects of cyanidin-3-O-glucoside from blackberry extract against peroxynitrite-induced endothelial dysfunction and vascular failure. *Life Sciences*, 73(9), 1097-1114. doi:10.1016/s0024-3205(03)00356-4
- Sewram, V., Raynor, M. W., Mulholland, D. A., & Raidoo, D. M. (2001). Supercritical fluid extraction and analysis of compounds from *Clivia miniata* for uterotonic activity. *Planta Medica*, 67(5), 451-455. doi:10.1055/s-2001-15801
- Si, H., Wyeth, R. P., & Liu, D. (2014). The flavonoid luteolin induces nitric oxide production and arterial relaxation. *European Journal of Nutrition*, 53(1), 269-275. doi:10.1007/s00394-013-0525-7
- Silva, F. S., Menezes, P. M., de Sá, P. G., Oliveira, A. L., Souza, E. A., Almeida, J. R.,...Lucchese, A. M. (2016). Chemical composition and pharmacological properties of the essential oils obtained seasonally from *Lippia thymoides*. *Pharmaceutical Biology*, 54(1), 25-34. doi:10.3109/13880209.2015.1005751
- Singh, M. K., Savita, K., Singh, S., Mishra, D., Rani, P., Chanda, D., & Verma, R. S. (2023). Vasorelaxant property of 2-phenyl ethyl alcohol isolated from the spent floral distillate of damask rose (*Rosa damascena* Mill.) and its possible mechanism. *Journal of Ethnopharmacology*, 313, 116603. doi:10.1016/j.jep.2023.116603
- Singh, T. U., Kathirvel, K., Choudhury, S., Garg, S. K., & Mishra, S. K. (2010). Eicosapentaenoic acid-induced endothelium-dependent and -independent relaxation of sheep pulmonary artery. *European Journal of Pharmacology*, 636(1-3), 108-13. doi:10.1016/j.ejphar.2010.02.041
- Singh, T. U., Garg, S. K., & Mishra, S. K. (2012). Evaluation of effects of eicosapentaenoic acid on $\text{Na}^+\text{-K}^+\text{-ATPase}$ in sheep pulmonary artery. *Human & Experimental Toxicology*, 31(6), 579-87. doi:10.1177/0960327111417909

- Skalicka-Woźniak, K., Mendel, M., Chłopecka, M., & Dziekan, N. (2016). Isolation and evaluation of the myorelaxant effect of bergapten on isolated rat jejunum. *Pharmaceutical Biology*, 54(1), 48-54. doi:10.3109/13880209.2015.1014570
- Son, N. T., Gianibbi, B., Panti, A., Spiga, O., Bastos, J. K., & Fusi, F. (2024). Vasorelaxant activity of (2S)-sakuranetin and other flavonoids isolated from the green propolis of the caatinga *Mimosa tenuiflora*. *Planta Medica*, 90(6), 454-468. doi:10.1055/a-2294-7042
- Sthijns, M. M. J. P. E., Schiffrers, P. M., Janssen, G. M., Lemmens, K. J. A., Ides, B., Vangrieken, P.,... Haenen, G. R. M. M. (2017). Rutin protects against H₂O₂-triggered impaired relaxation of placental arterioles and induces Nrf2-mediated adaptation in human umbilical vein endothelial cells exposed to oxidative stress. *Biochimica et Biophysica Acta. General Subjects*, 1861(5 Pt A), 1177-1189. doi:10.1016/j.bbagen.2017.03.004
- Tamaoki, J., Kanemura, T., Horii, S., Chiyotani, A., Sakai, N., Kobayashi, K., & Takizawa, T. (1990). Relaxation of canine airway smooth muscle by the heparin preservative benzyl alcohol. *American Physiological Society Journal*, 258(6 Pt 1), L355-L360. doi:10.1152/ajplung.1990.258.6.l355
- Tarlacı, S. (2021). A new source of omega-3 and gamma tocopherol: Fig (*Ficus carica* L.) seed oil. *Harran Tarım ve Gıda Bilimleri Dergisi*, 25(4), 556-560. doi:10.29050/harranziraat.806278
- Tas, E. N. (2019). Biochemical characterization of Fig (*Ficus carica* L.) seeds. *Journal of Agricultural Sciences*, 25, 232-237. doi:10.15832/ankutbd.398268
- Tom, E. N., Girard-Thernier, C., & Demougeot, C. (2016). The Janus face of chlorogenic acid on vascular reactivity: A study on rat isolated vessels. *Phytomedicine*, 23(10), 1037-42. doi:10.1016/j.phymed.2016.06.012
- Ustun-Argon, Z., Sari, Z., Gokyer, A., & Buyukhelvacigil-Ozturk, S. (2021). Phytochemical evaluation of *Ficus carica* seeds and their cold pressed oil. *Journal of Pharmaceutical Research*, 20(4), 71-79. doi:10.18579/jopcr/v20i4.2
- Venkateswarlu, K., Dange, S. Y., & Manchanda, R. (1999). Effects of heptanol on the neurogenic and myogenic contractions of the guinea-pig vas deferens. *British Journal of Pharmacology*, 126(1), 227-234. doi:10.1038/sj.bjp.0702307
- Verspohl, E. J., Ploch, M., Windeck, T., Klaes, M., Schmidt, T., & Bauer, K. (2008). Effect of two artichoke extracts (36_U and 36_EB) on rat ileum (with respect to bowel syndrome) and the peristaltic threshold. *Phytomedicine*, 15(11), 1002-1009. doi:10.1016/j.phymed.2008.02.011
- Versteeg, N., Wellauer, V., Wittenwiler, S., Aerenhouts, D., Clarys, P., & Clijsen, R. (2024). Short-term cutaneous vasodilatory and thermosensory effects of topical methyl salicylate. *Frontiers in Physiology*, 15, 1347196. doi:10.3389/fphys.2024.1347196
- Wahid, M., Saqib, F., Qamar, M., & Ziora, Z. M. (2022). Antispasmodic activity of the ethanol extract of *Citrullus lanatus* seeds: Justifying ethnomedicinal use in Pakistan to treat asthma and diarrhea. *Journal of Ethnopharmacology*, 295, 115314. doi:10.1016/j.jep.2022.115314
- Wang, D., Hou, J., Wan, J., Yang, Y., Liu, S., Li, X.,... Wang, P. (2021). Dietary chlorogenic acid ameliorates oxidative stress and improves endothelial function in diabetic mice via Nrf2 activation. *Journal of International Medical Research*, 49(1), 300060520985363. doi:10.1177/0300060520985363

- Wang, H. W., Liu, S. C., Chao, P. Z., & Lee, F. P. (2016). Menthol inhibiting parasympathetic function of tracheal smooth muscle. *International Journal of Medical Sciences*, 13(12), 923-928. doi:10.7150/ijms.17042
- Wang, Q., Zhang, X., & Kang, J. (1997). Effects of 8-methoxypsoralen on smooth muscle of isolated human pulmonary arteries. *Zhonghua Jie He He Hu Xi Za Zhi*, 20(4), 222-224.
- Wang, W., Wu, Q. H., Sui, Y., Wang, Y., & Qiu, X. (2017). Rutin protects endothelial dysfunction by disturbing Nox4 and ROS-sensitive NLRP3 inflammasome. *Biomedicine & Pharmacotherapy*, 86, 32-40. doi:10.1016/j.biopha.2016.11.134
- Wang, Y., Wang, X. J., Zhao, L. M., Pang, Z. D., She, G., Song, Z.,...Deng, X. L. (2019). Oxidative stress induced by palmitic acid modulates KCa2.3 channels in vascular endothelium. *Experimental Cell Research*, 383(2), 111552. doi:10.1016/j.yexcr.2019.111552
- Wang, Z., Song, M., Wang, Z., Chen, S., & Ma, H. (2021). Metabolome and transcriptome analysis of flavor components and flavonoid biosynthesis in fig female flower tissues (*Ficus carica* L.) after bagging. *BMC Plant Biology*, 21(1), 396. doi:10.1186/s12870-021-03169-1
- Wei, J., Takeuchi, K., & Watanabe, H. (2013). Linoleic acid attenuates endothelium-derived relaxing factor production by suppressing cAMP-hydrolyzing phosphodiesterase activity. *Circulation Journal*, 77(11), 2823-30. doi:10.1253/circj.cj-13-0248
- Yang, M., Zhou, Y., Wan, L. L., Ye, J. Z., Lu, H. L., Huang, X., & Xu, W. X. (2020). Luteolin suppresses colonic smooth muscle motility via inhibiting L-type calcium channel currents in mice. *General Physiology and Biophysics*, 39(1), 49-58. doi:10.4149/gpb_2019045
- Ybañez-Julca, R. O., Pino-Ríos, R., Quispe-Díaz, I. M., Asunción-Alvarez, D., Acuña-Tarrillo, E. E., Mantilla-Rodríguez, E.,...Benites, J. (2023). Antispasmodic effect of *Valeriana pilosa* root essential oil and potential mechanisms of action: Ex vivo and in silico studies. *Pharmaceutics*, 15(8), 2072. doi:10.3390/pharmaceutics15082072
- Zhang, W., Fu, F., Tie, R., Liang, X., Tian, F., Xing, W.,...Zhang, H. (2013). Alpha-linolenic acid intake prevents endothelial dysfunction in high-fat diet-fed streptozotocin rats and underlying mechanisms. *Vasa*, 42(6), 421-8. doi:10.1024/0301-1526/a000311
- Zhang, X., Mao, A., Xiao, W., Zhang, P., Han, X., Zhou, T.,...Ma, X. (2019). Morin induces endothelium-dependent relaxation by activating TRPV4 channels in rat mesenteric arteries. *European Journal of Pharmacology*, 859, 172561. doi:10.1016/j.ejphar.2019.172561
- Zhou, Z. Y., Xu, J. Q., Zhao, W. R., Chen, X. L., Jin, Y., Tang, N., & Tang, J. Y. (2017). Ferulic acid relaxed rat aortic, small mesenteric and coronary arteries by blocking voltage-gated calcium channel and calcium desensitization via dephosphorylation of ERK1/2 and MYPT1. *European Journal of Pharmacology*, 815, 26-32. doi:10.1016/j.ejphar.2017.10.008
- Zhu, X. M., Fang, L. H., Li, Y. J., & Du, G. H. (2007). Endothelium-dependent and -independent relaxation induced by pinocembrin in rat aortic rings. *Vascular Pharmacology*, 46(3), 160-165. doi:10.1016/j.vph.2006.09.003